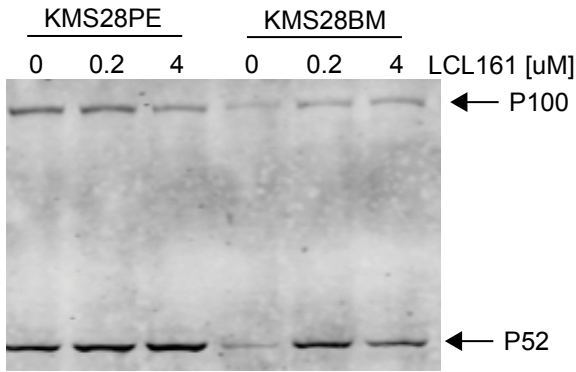
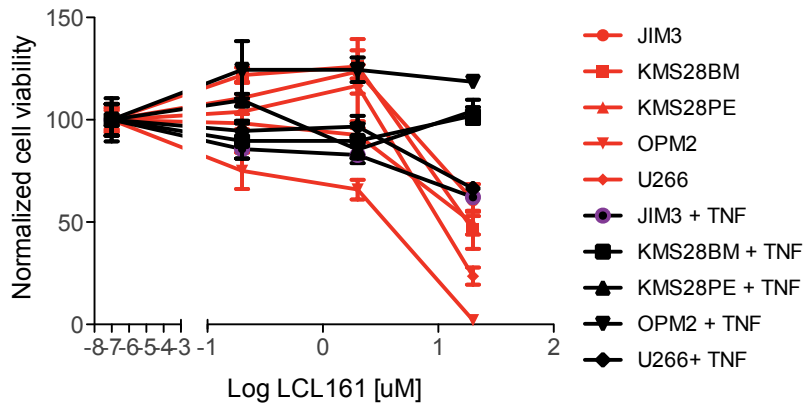


a**b**

Supplementary Figure 1. LCL161 activates NFκB2 and is not directly cytotoxic against myeloma cells at clinically relevant concentration. a) Western blot analysis for NF-κB2 in human myeloma cell lines (HMCLs) treated for 18 hours with the indicated LCL161 concentration. KMS28PE, harboring a biallelic deletion of cIAP1/2, has constitutively high levels of p52, which are not further induced by LCL161 treatment compared to the isogenic KMS28BM expressing cIAP1/2. **b)** Proliferation assay of the indicated HMCLs grown for 72hrs in the presence of increasing LCL161 concentration with or without TNF 50ng/ml. Cell viability was measured in quadruplicate by Cell Titer Glo assay and is shown normalized to vehicle controls. Error bars indicate mean with standard deviation.

PPV=73%

NPV=92%

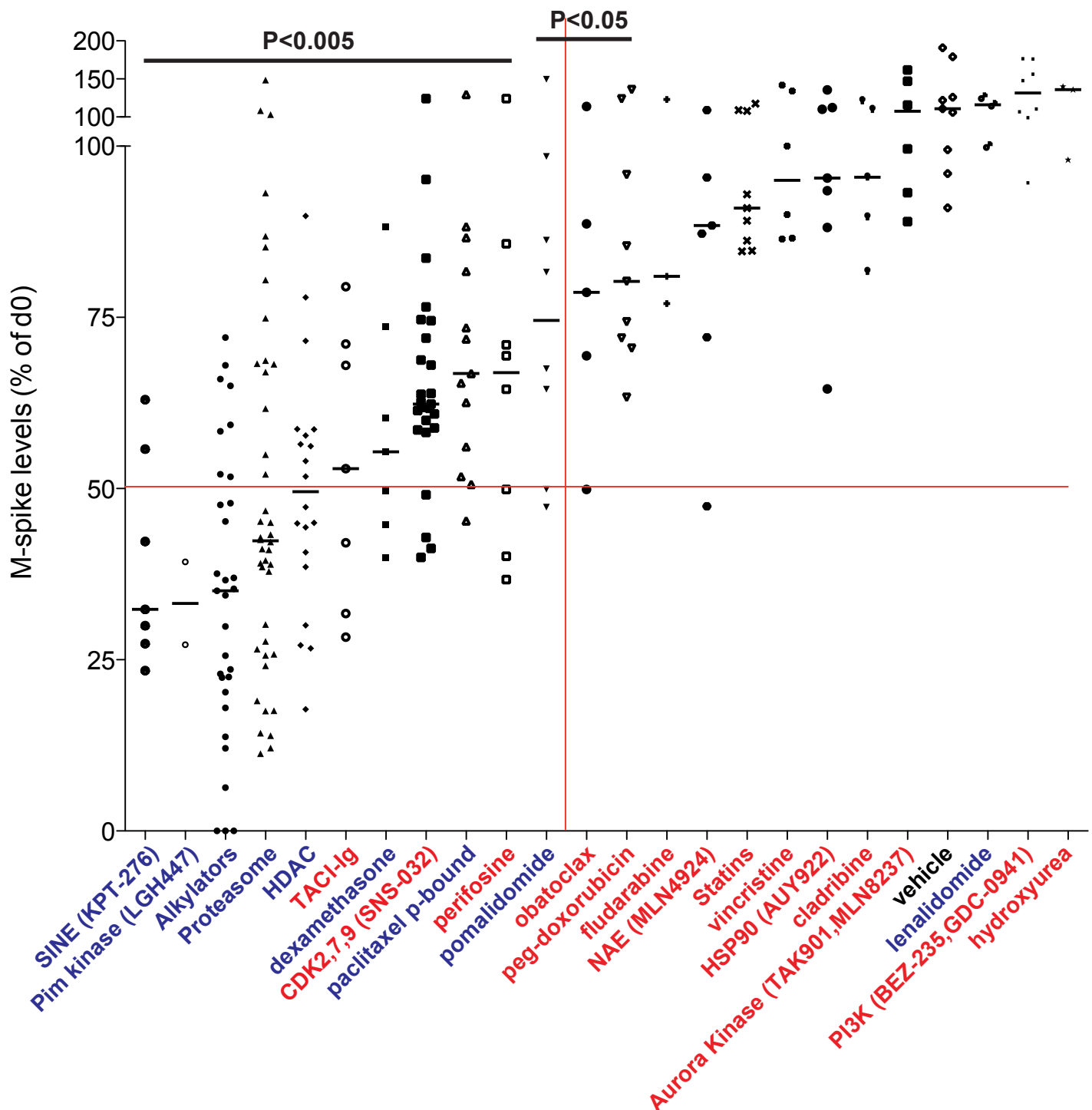
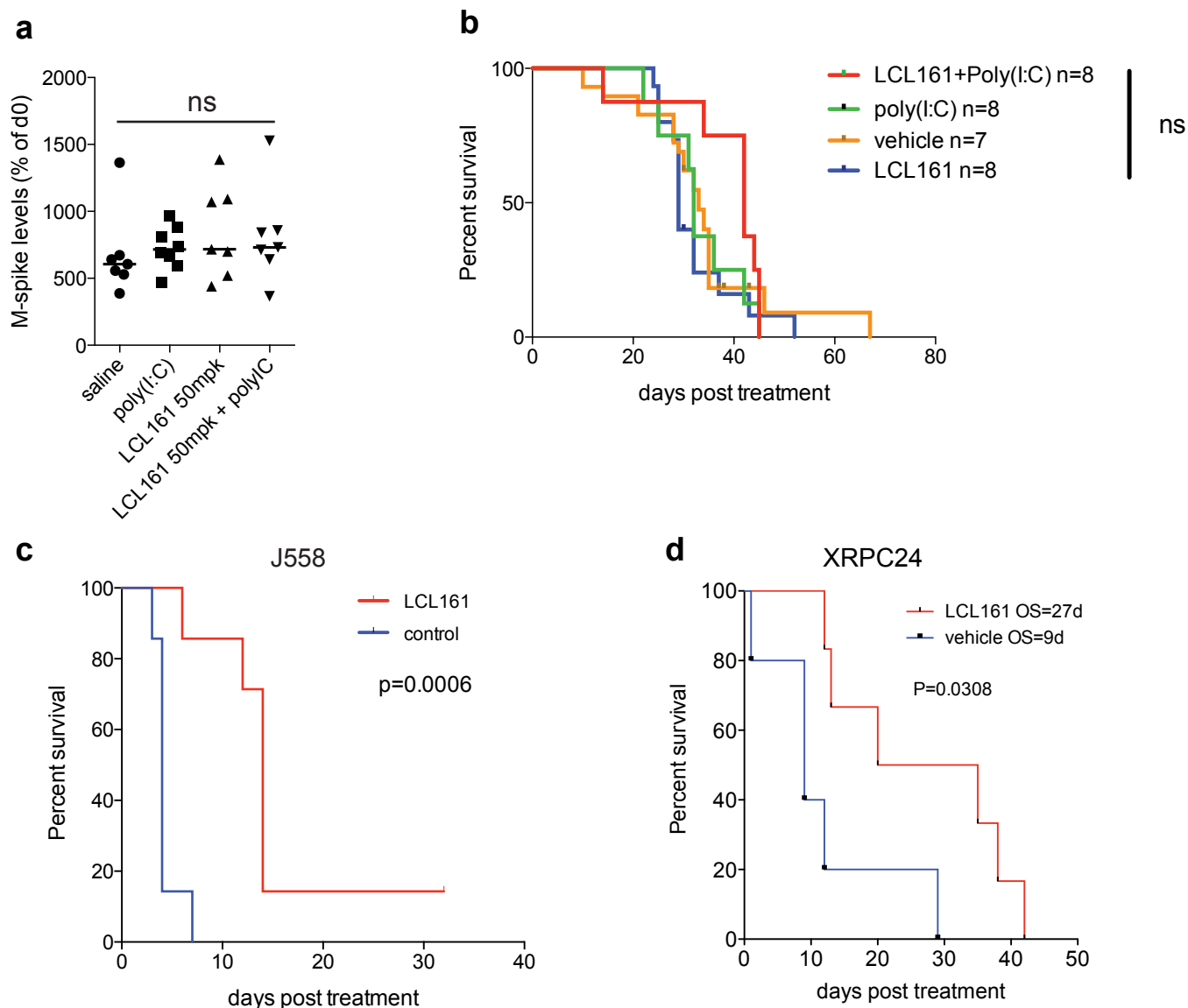
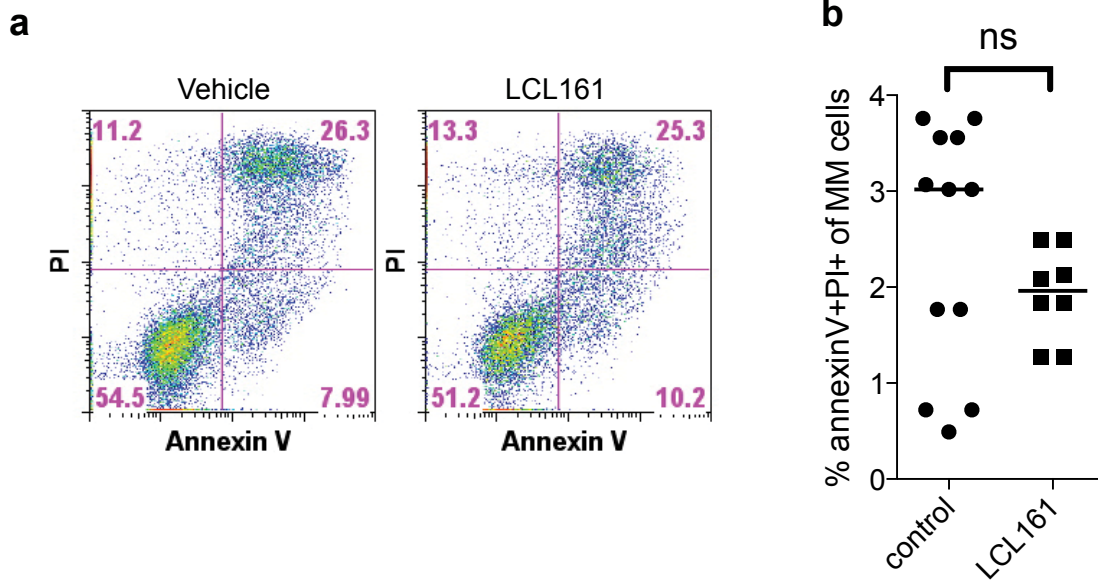


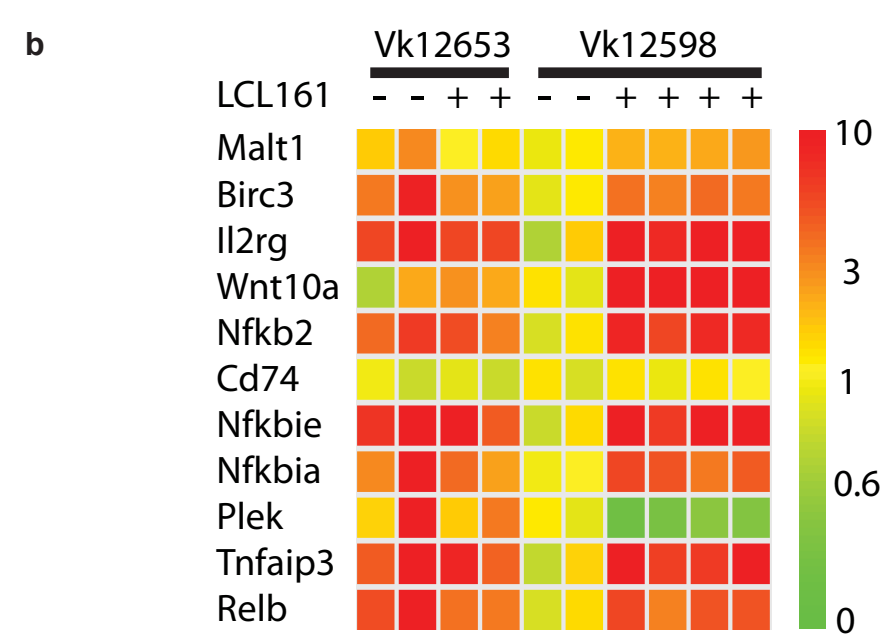
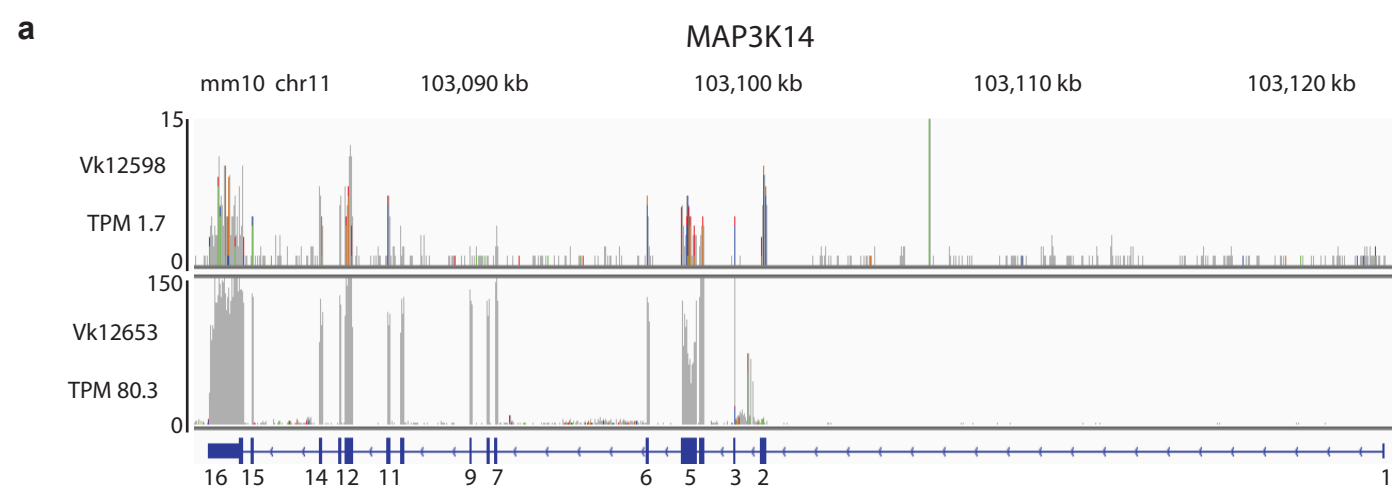
Figure S2. The response of Vk*MYC mice to drugs with known activity in patients with multiple myeloma. M-spike levels were measured in *de novo* Vk*MYC mice with MM after two weeks of treatment with the indicated drugs, and normalized to day0. Each dot represents an individual M-spike. Horizontal black bars show median M-spike levels. Drugs with single agent response rates demonstrated in MM clinical trials above 10%, or superior activity in combination are labeled in blue, others in red. A red horizontal line identifies the cut-off for response (>50% M-spike reduction). A vertical red line separate active (>20% response rate, on the left) from inactive (on the right) regimens. The parametric unpaired two-tailed *t* test *P* value of active drugs compared to vehicle is shown. Out of 11 classes of drugs active in this model, eight are clinically active (response rate >20% as single agent, or superior activity in combination) for a positive predictive value (PPV) of 73%. Out of 12 classes of drugs inactive in this model, 11 are also clinically inactive, for a negative predictive value (NPV) of 92%.



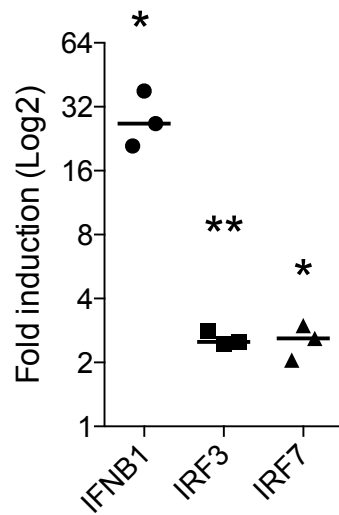
Supplementary Figure 3. Anti tumor activity of LCL161. **a)** M-spike levels in Vk12653 tumor bearing mice were measured at day 14 and normalized to day0 levels after treatment with saline, Poly(I:C) 2.5mg/kg by intra-peritoneal injection, LCL161 50mg/kg orally or the combination on days 1,4,8,11. Each dot represent a treated mouse. Horizontal black bars indicate median M-spike levels. **b)** Kaplan-Meier survival plot for mice described in a). The number of treated mice (*n*) is indicated. Balb/c mice transplanted **c)** sub-cutaneously with the murine plasmacytoma cell line J558 or **d)** intra-venously with XRPC24 received vehicle (*n*=7) or LCL161 100mg/kg twice/week for two weeks (*n*=7) beginning ~4 weeks post transplantation. *P* values for Log-rank (Mantel-Cox) test are shown.



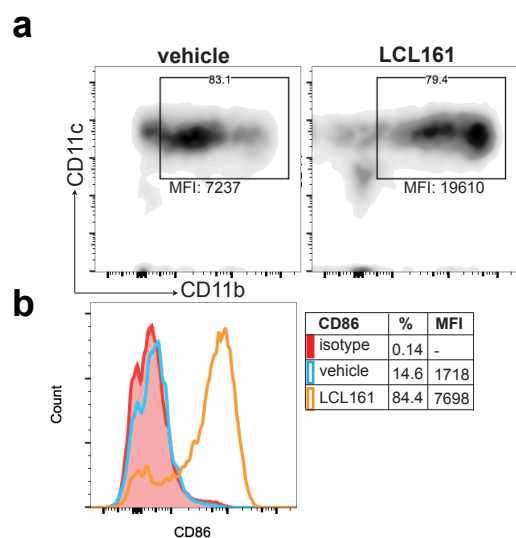
Supplementary Figure 4. LCL161 is not cytotoxic to Vk12598 MM cells. **a)** Viability of CD138+ MM cells harvested from Vk12598 tumor bearing mice, isolated by magnetic selection and exposed in vitro for 18hrs to vehicle or LCL161 200nM was evaluated by flow cytometric analysis using annexin-V and propidium iodine (PI) staining following manufacturer's recommendations. A representative example out of three experiments is shown. **b)** Viability of CD19-CD138+ MM cells harvested from Vk12598 tumor bearing mice after exposure overnight to vehicle or LCL161 100mg/kg was evaluated by annexinV/PI staining. Each dot represents a sampled mouse; bars indicate median levels.



Supplementary Figure 5. MAP3K14 (NIK) dysregulation by IAP LTR in Vk12653. RNA Sequencing of BM CD138-selected cells from mice transplanted with Vk12598 and Vk12653BM was performed using Illumina paired-ends with six samples per lane of a HiSeq 2000. **a)** Number of reads aligning to each base-pair of the MAP3K14 gene. The level of transcription of MAP3K14 as measured by transcript per million (TPM) is 50-fold higher in VK12653 (80.3 TPM) compared to Vk12598 (1.7 TPM), leading to a different scale for the number of reads. The alignment in Vk12653 identifies a lack of transcription of exons 1 and 2, and high level transcription of exons 3 to 16. The reads upstream of exon 3 in Vk12653 originate from an Intracisternal A Particle Long Terminal Repeat that maps to multiple loci in the genome, including for example chr2:151205295-151205463. **b)** Heat map representation of gene expression obtained from RNAseq data from Vk12653 and Vk12598 tumor bearing mice treated or not with LCL161. All of the samples were normalized to the level of expression in untreated Vk12598. Consistent with constitutive activation of NFkB there is a very high level of basal transcription of NFkB target genes (from Annunziata et al. Cancer Cell 2007) in Vk12653 that is not induced further by LCL161.



Supplementary Figure 6. LCL161 treatment induces type I IFN response *in vitro*. Expression of the indicated genes was assessed by qPCR analysis in triplicate on cDNA harvested from the J558 balb/c plasmacytoma cell line treated *in vitro* for 18 hrs with 0.5uM LCL161 and it is shown normalized to polR2a gene, relatively to vehicle control. Each dot represents a tested sample. Bars indicate median levels. One sample two sided *t* test *P* values are shown for comparison .

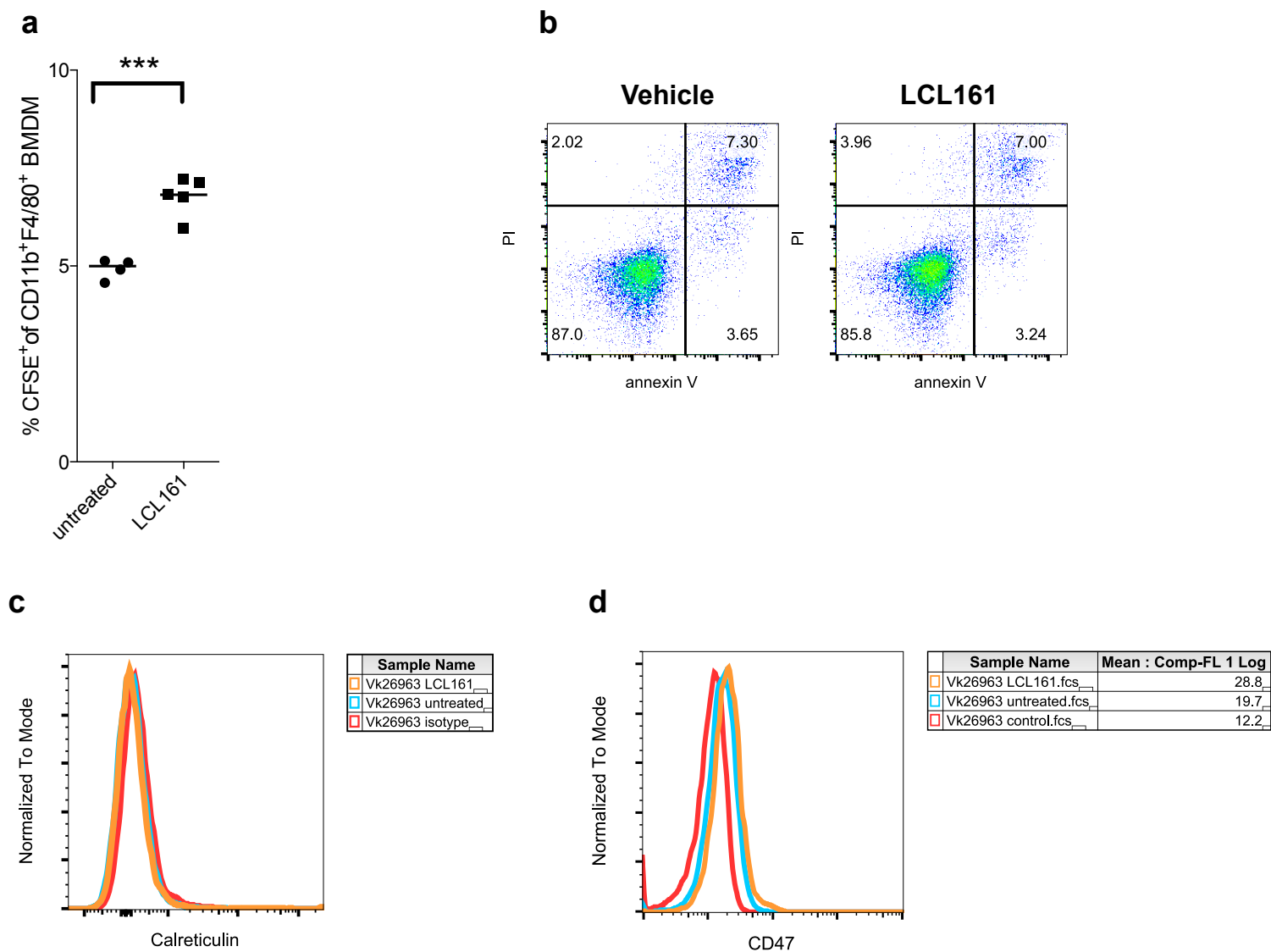


Supplementary Figure 7. LCL161 activates in vitro generated dendritic cells. Expression of the activation markers **a**) CD11b and **b**) CD86 was evaluated by flow cytometry in dendritic cells generated in vitro by stimulation for eight days with flt3, after 4hrs treatment with vehicle or 200nM LCL161. The percentage of CD11b⁺CD11c⁺ and median fluorescence intensity (MFI) for CD11b⁺ cells is reported in the dot plot panels for one representative example of two independent experiments. Histogram plot shows CD86 expression (% and MFI) for CD11b⁺CD11c⁺

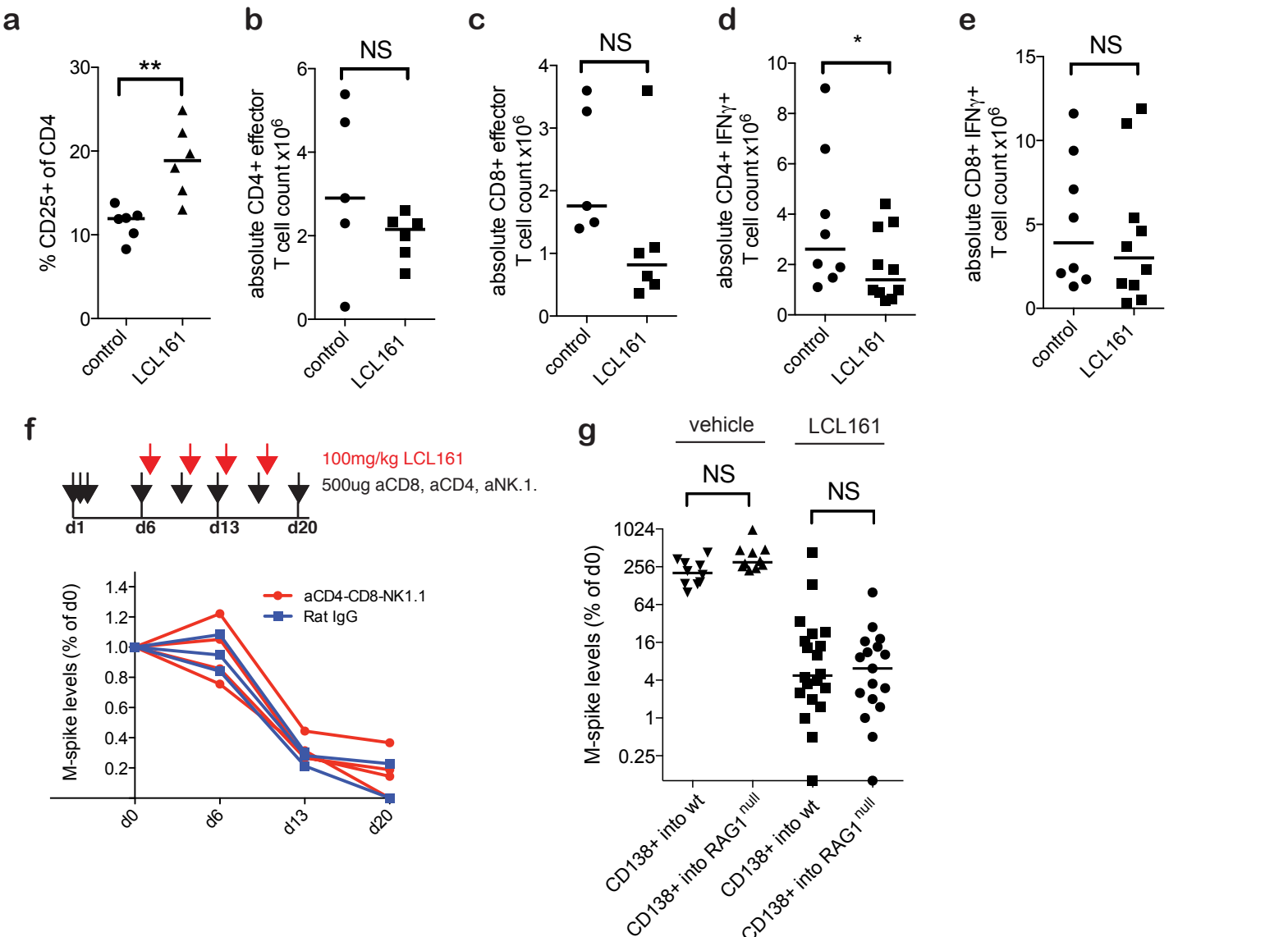
	IL-8	MCP-1	IL-6	IL-12	IL-1B	IL-10	IFNa	IP-10	MIP-1B	IL-2	MIG	IL-15	MIP-1a	GM-CSFEOTAXIN	IL-17	IL-1RA	TNFa	IL-2R	IL-4	IFNg	IL-5	IL-7	
MC2217	5.9	1.6	1.0	1.2	1.1	1.3	1.3	0.9	1.0	1.1	0.9	0.9	0.9	1.6	1.0	1.0	1.0	0.9	1.2	0.8	1.0	0.8	0.9
MC2119	5.2	1.6	1.6	1.5	1.1	1.7	1.3	2.2	1.2	1.2	1.1	1.4	1.1	1.0	1.3	1.6	0.9	0.9	0.8	1.8	1.0	4.3	1.1
MC2069	3.8	1.8	1.6	1.3	1.1	1.6	1.2	1.0	1.2	1.3	0.9	1.6	1.2	4.4	1.3	2.1	1.0	1.0	1.1	1.3	0.9	0.6	1.3
MC1494	14.8	1.7	1.6	1.8	3.0	1.1	1.4	1.0	1.2		0.8	0.8	0.9	1.0	0.6	0.8	1.1	1.0	1.0	1.0	0.9	0.5	0.5
MC1955	24.4	2.7	2.4	1.5	1.0	1.2	1.6	1.3	1.2	1.4	1.3	1.1	1.1	1.0	1.2	1.3	1.1	1.1	0.9	0.8	1.1	0.9	0.8
MC1870	11.7	2.1	1.3	1.5	1.4	1.1	1.5	1.3	1.5		1.2	1.0	1.0	0.9		1.3	1.1	0.9	1.0	0.9	0.8	0.8	0.7
MC1755	16.6	2.3	2.1	1.6	1.1	1.1	1.4	1.0	1.2		1.1	1.1	1.0	1.0	0.8	0.9	1.0	0.8	0.9	0.9	1.0	0.5	0.4
MC2638	61.3	4.1	1.4	1.4	0.9	1.3	2.2	1.3	1.4	1.3	1.1	0.8	1.2	1.0	1.2	1.0	1.0	1.0	1.1	1.3	0.9	1.3	0.8
MC2655	2.8	1.3	1.0	1.2	1.2	1.1	0.9	1.1	0.9	0.5	1.1	1.1	1.0	1.1	0.9	0.9	1.1	0.8	0.8	0.9	1.0	0.7	0.3
MC2069	13.4	2.0	1.0	1.2	1.6	1.2	1.3	1.1	1.1	1.4	1.0	1.1	1.0	1.1	0.9	1.4	1.0	0.8	0.8	1.1	1.0	1.0	0.9
MC2702	3.0	1.3	1.2	1.2	0.9	0.7	1.2	1.1	1.0		1.2	1.1	1.0	1.1	0.9	0.7	1.0	1.0	1.0	1.1	1.0	0.6	0.6



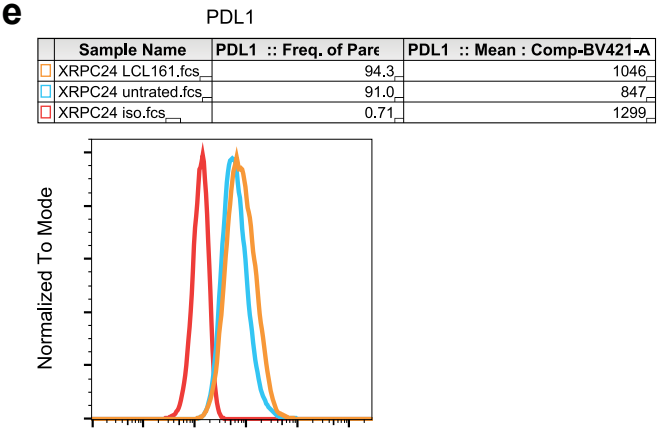
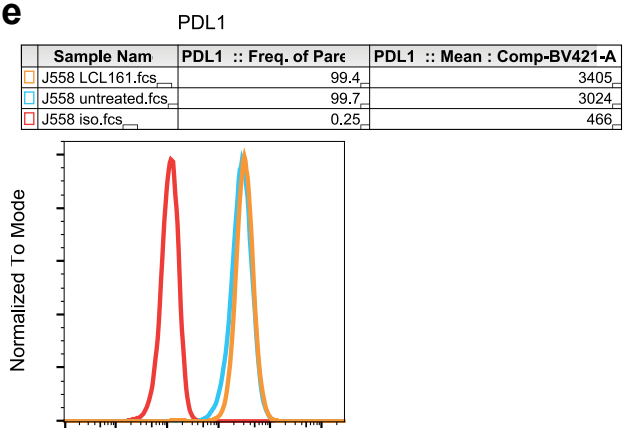
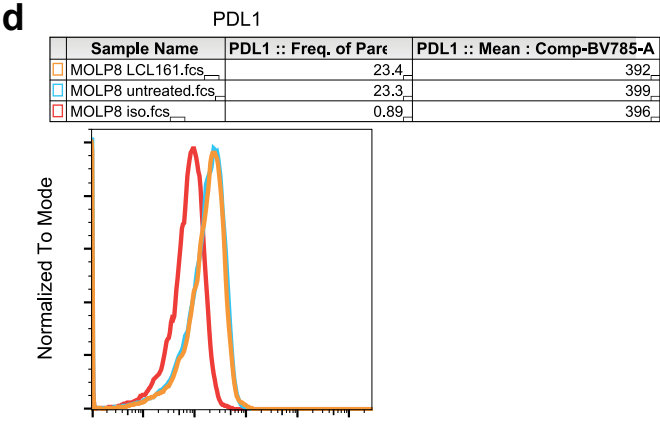
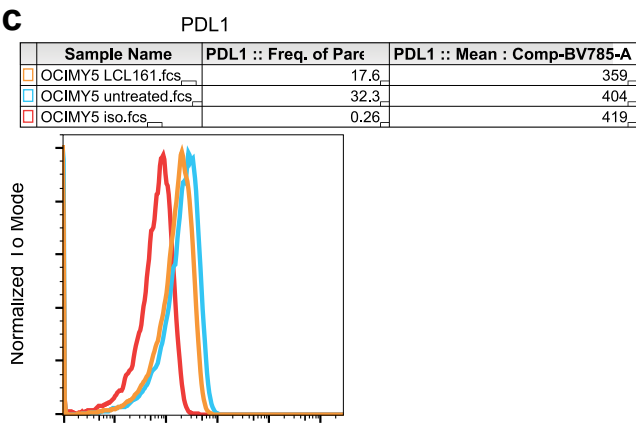
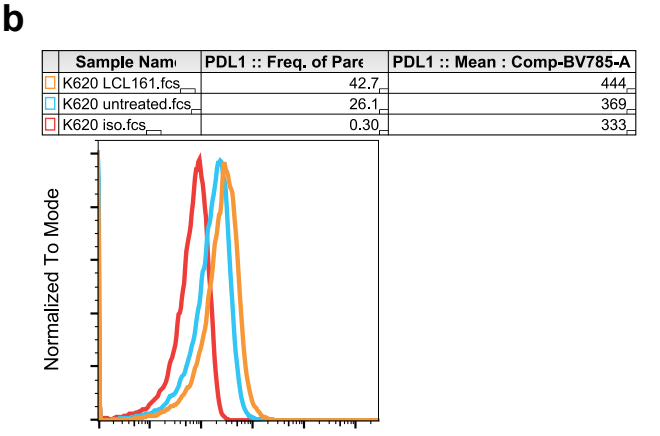
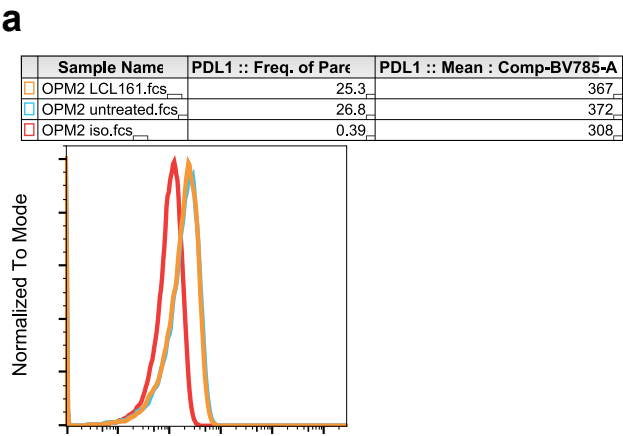
Supplementary Figure 8. LCL161 induces inflammatory cytokines expression detected in the plasma of MM patients. Heat map of cytokine levels assayed in duplicate using the Cytokine Human 30-Plex Panel for Luminex® Platform (LHC0003, Thermo Fisher Scientific) in peripheral blood plasma collected from MM patients four hours after the first day of single agent LCL161 treatment, shown normalized to the baseline levels. Color scale from 0.5 to 5 fold induction is shown. Each horizontal line represents the normalized cytokine values from an patient, tested in duplicate.



Supplementary Figure 9. LCL161 treatment increases phagocytosis of Vk26963 lymphoma cells without inducing apoptosis. **a)** Phagocytic activity, measured as percentage of CFSE⁺ bone marrow derived macrophages (BMDM) after IFN γ priming overnight and exposure for two hours to CFSE labeled Vk26963 cells treated or not with LCL161 200nM. The percentage of live, single, CFSE⁺ cells in the CD11b⁺F4/80⁺ macrophage gate is shown. Bars indicate median levels and unpaired two-tailed t test statistical values are shown. Each dot represent a tested well from a representative experiment out of two performed. **b)** Viability staining of Vk26963 cells after treatment for 24 hours with LCL161 200nM. Annexin-V and PI expression were analyzed by flow cytometry. Percentage of Annexin V - PI gates is shown for a representative experiment, repeated three times. The same cells were alternatively stained with **c)** unconjugated anti-calreticulin, followed by secondary anti-rabbit IgG or **d)** anti-CD47 and analyzed by flow cytometry. Histograms show overlay of isotype controls (red line), untreated (blue) or LCL161 treated (orange) Vk26963 cells. Medianfluorescence CD47 intensity is shown.



Supplementary Figure 10. LCL161 anti-myeloma short-term activity is independent of adaptive immunity. **a)** The fraction of splenic CD4+ T-cells that are CD25+ is shown for Vk12598 MM bearing mice that received vehicle or LCL161 at 50mg/kg at day 1 and 4, collected seven days after the initiation of the treatment. Absolute numbers of splenic **b)** CD4 and **c)** CD8 T-cell effector subsets (CD62L-CD44+) and IFN γ producing **d)** CD4 and **e)** CD8 T-cells from Vk12598 tumor bearing mice treated as in **a)**. Each dot represents a treated mouse. Bars indicate median values. t test p values are shown for the data points. **f)** M-spikes levels following treatments are shown normalized to day 0 for six aged *de novo* Vk*MYC mice receiving either rat IgG (blue lines) or blocking antibodies against CD8, CD4 or NK.1 (red lines) together with LCL161 at the indicated time. **g)** M-spike levels were measured after two weeks of vehicle or LCL161 treatment and shown normalized to day0 in Wt or RAG1null mice engrafted with CD138+ Vk12598 myeloma cells. Each dot represents a treated mouse. Bars show median M-spike levels. *P* values for parametric unpaired two sided t tests are shown.



Supplementary Figure 11. PDL1 expression in multiple myeloma. PDL1 expression evaluated by flow cytometry in **a)** CD11b+ myeloid cells or **b)** CD19-CD138+ MM cells harvested from Vk12598 tumor bearing mice after 18hrs treatment with vehicle or LCL161 200nM. Each dot represent a mouse; bars indicate median levels; results from unpaired prametric two-tailed *t* test are shown. PDL1 expression (% positive and MFI) in human myeloma cell lines (**c-e**) or murine Balb/c plasmacytoma lines (**g-h**) untreated (blue line) or treated overnight with LCL161 200nM (orange line). Examples from two independent experiments are shown.

Supplementary Table 1. Patient baseline characteristics

	Total (25)
Age	
Median	68.0
Range	47.0 – 90.0
Gender	
Female	9 (36%)
Male	15 (64%)
Months from Diagnosis to On Study	
Median	46.2
Range	11.3 – 99.1
High risk features (t(4;14), del17p, add 1q, S-phase>3%)	
One or more present	11 (44%)
None	14 (56%)
Number of prior regimens	
Median	3.0
Range	(1.0 – 6.0)
Disease status	
Relapsed	7 (28%)
Relapsed and Refractory	18 (72%)
Previous Transplant	18 (72%)

Supplementary Table 2. Toxicity

Adverse Event		Grade							
		1		2		3		4	
		N	%	N	%	N	%	N	%
Type									
Anemia		13	52.0	5	20.0	6	24.0		
Fatigue		8	32.0	12	48.0	4	16.0		
Nausea		10	40.0	8	32.0	1	4.0		
Platelet count decreased		13	52.0	2	8.0	2	8.0	1	4.0
Neutrophil count decreased		1	4.0	7	28.0	7	28.0	2	8.0
Peripheral sensory neuropathy		11	44.0	6	24.0				
Lymphocyte count decreased				2	8.0	7	28.0	6	24.0
Lymphocyte count increased				1	4.0	2	8.0		
White blood cell decreased				7	28.0	3	12.0	2	8.0
Vomiting		8	32.0	5	20.0	1	4.0		
Pruritus		10	40.0	2	8.0				
Constipation		9	36.0	2	8.0				
Cough		8	32.0	3	12.0				
Diarrhea		7	28.0	3	12.0	1	4.0		
Anorexia		9	36.0	1	4.0				
Dyspnea		6	24.0	4	16.0				
Rash maculo-papular		8	32.0	1	4.0	1	4.0		
Fever		6	24.0	2	8.0				
Edema limbs		7	28.0						
Abdominal pain		2	8.0	4	16.0				
Cytokine release syndrome				4	16.0				
Peripheral motor neuropathy		4	16.0						
Hyperglycemia						3	12.0		
Syncope						3	12.0		
Hyperuricemia								1	4.0
Hypotension						1	4.0		
Lung infection						1	4.0		
Pain in extremity						1	4.0		
Sepsis								1	4.0
Urticaria						1	4.0		

All grade 3+ toxicities, as well as all toxicities occurring in more than one patient.

Supplementary Table S3. Genes induced in MM cells from both Vk12598 tumor-bearing mice and patients following *in vivo* treatment with LCL161, ranked by fold induction in Vk12598

#	Vk12598
Ifit3	23.64
Cd40	12.86
Anxa2	12.24
Gbp2	11.91
Cfb	10.51
Tnfaip3	9.769
Nfkbie	9.167
Il2rg	6.853
Irf7	6.465
Icam1	6.14
Relb	5.335
Lgals3	5.2
Ahnak	4.926
Gbp5	4.817
Nfkbia	4.792
Nfkb2	4.739
Ikbke	4.627
Parp14	4.15
Tuba1a	3.783
Egr1	3.762
Birc3	3.758
Rnf19b	3.686
Bcl3	3.661
Isg15	3.456
Stx11	3.449
Ube2l6	3.243
Gbp3	3.241
Sat1	3.219
Pim1	3.147
Tmem106a	3.106
Hspb1	3.029
Ifitm3	3.023
Tubb6	2.87
Map4	2.811
Slc19a2	2.789
Junb	2.788
Tmsb10	2.788
Rnf213	2.737
Rasgrp1	2.654
Gadd45a	2.642
Flna	2.618
Ifitm2	2.572
Ddx58	2.536

Trib3	2.533
Parp10	2.419
Trib1	2.417
Parp9	2.402
Gadd45b	2.356
Chst11	2.312
Ier2	2.307
Dusp2	2.279
Sp100	2.276
Dtx3l	2.247
Eif2ak2	2.189
Lgals1	2.18
Herc6	2.142
Plagl2	2.133
Cflar	2.126
Casp1	2.106
Dlgap4	2.096
Arid5a	2.058
Capn2	2.047
Maff	2.043
Nfkbiz	2.037
Dram1	2.032
Mapkapk2	2.023
MLkl	2.016
Tom1	2.012
Cth	2.003
Mapk6	1.995
Ifrd1	1.95
Fkbp5	1.931
N4bp2l1	1.9
Slc25a20	1.896
Syng2	1.887
Fam83g	1.884
Jund	1.882
Spint1	1.87
Runx1	1.853
Shisa5	1.841
Adm2	1.838
Bfsp2	1.836
Rap1b	1.836
Trex1	1.827
Fosl2	1.824
Cmpk2	1.814
Jdp2	1.801
Zfand5	1.799
Capg	1.791
Ppp1r15a	1.779
Sh3bgrl3	1.777

Ticam1	1.764
S100a11	1.748
Cd97	1.741
Rtkn	1.739
Isg20	1.735
Bcap29	1.721
Ppp4r1	1.719
Ddit4	1.715
Bcl2l11	1.711
Cpt1a	1.705
Lsm7	1.69
Pfkfb3	1.688
Pde4b	1.684
Zmiz2	1.682
Tagln2	1.673
Wdfy1	1.667
Ldlr	1.664
Klf16	1.662
Myadm	1.661
Tuba1c	1.661
Arhgap23	1.658
Vat1	1.657
Gbp4	1.646
Notch2	1.643
Efhd2	1.64
Mvp	1.639
Acadvl	1.636
Pgd	1.634
Csnk1g1	1.628
Nedd9	1.626
Traf2	1.625
Slc25a19	1.624
Trim56	1.624
Ifi35	1.615
Tnks1bp1	1.614
Fam49b	1.61
Cast	1.604
Slc27a4	1.602
Nbeal2	1.594
Atf5	1.591
Vav2	1.589
Cebpb	1.583
Chchd10	1.57
Tor3a	1.57
Psen2	1.566
Nfe2l1	1.564
Ube2f	1.561
Rara	1.556

Zc3h12a	1.546
Abl2	1.543
Arpc1b	1.543
Sbno2	1.537
Bcl10	1.533
Rasa2	1.522
Actr3	1.517
Etfdh	1.517
Eif6	1.513
Bik	1.51
Smap2	1.506
Samhd1	1.499
Sft2d2	1.498
Angptl6	1.492
Cdkn2aipnl	1.492
Nfkbib	1.489
Tfe3	1.483
Stat6	1.481
Rnf149	1.48
Ufsp1	1.48
Tap1	1.477
Kpna4	1.471
Hmgcs1	1.468
Ninj1	1.465
Map7d1	1.459
Fam35a	1.451
Prdm1	1.449
Lmna	1.442
Slc31a2	1.439
Trpv2	1.437
Lnpep	1.436
Slc7a5	1.434
Trim14	1.431
Lrrc8b	1.43
Stk40	1.429
Traf6	1.422
Coq10b	1.419
Tsc22d3	1.415
Arpc2	1.413
Asl	1.411
Nfkb1	1.41
Trim25	1.409
Tbk1	1.408
Fyco1	1.407
Elk1	1.406
Gsdmd	1.404
Peli1	1.401
Sri	1.4

Psmc1	1.399
Ehbp1l1	1.396
Acsl1	1.395
Mex3c	1.395
Ap1s2	1.394
Tmem55b	1.392
Mfsd2a	1.388
Nploc4	1.388
Pou2af1	1.387
Tfeb	1.387
Ptrh1	1.384
Etv3	1.383
Elmo1	1.382
Clip1	1.377
Bmf	1.374
Clic1	1.373
Hmgb3	1.372
Arid3a	1.371
Paqr4	1.371
Tap2	1.371
Sco2	1.37
Wars	1.37
Glrx	1.369
Ralb	1.368
Rnf19a	1.367
Slc39a1	1.367
Rragc	1.366
Psmc10	1.365
Map2k3	1.364
Arl8a	1.363
Phc2	1.357
Ccdc86	1.356
Ccdc88c	1.356
Lrrcc1	1.354
Pik3r1	1.354
Flot1	1.352
Med15	1.352
Tiparp	1.351
Myli1	1.35
Ube2o	1.35
Aldoa	1.349
Otud7b	1.349
Mrpl23	1.348
Klf7	1.347
Mllt11	1.346
Slc3a2	1.345
Tbpl1	1.343
Stat4	1.342

Nfil3	1.341
Ubap1	1.341
Tpm3	1.34
Acap2	1.339
Psma6	1.338
Chmp4b	1.337
Gnai3	1.337
Plxna1	1.334
Timm10	1.33
Eif4ebp1	1.329
Adnp2	1.327
Ddx10	1.327
Grk6	1.327
Tmem141	1.326
Fbxo6	1.325
Taf4b	1.324
Chrac1	1.323
Cytip	1.321
Rab21	1.321
Stat2	1.318
Acaa2	1.316
Aifm2	1.315
Esf1	1.312
Irf9	1.312
Armc7	1.311
Psmd4	1.311
Ino80c	1.309
Ezr	1.307
Psmd7	1.304
Hivep1	1.303
Rapgef2	1.302
Agfg1	1.298
Aida	1.298
Dnajc17	1.297
Siah2	1.296
B9d2	1.294
Baz1a	1.294
Trim24	1.293
Uhrf1bp1	1.293
Frg1	1.29
Slk	1.29
Atp1b3	1.289
Mtap	1.289
Cab39	1.288
Ppp1r7	1.288
Yod1	1.288
Naa20	1.287
Dnttip2	1.285

Ptpn1	1.285
Cd9	1.284
Psmc1	1.284
Rnf121	1.284
Got2	1.281
Kcmf1	1.28
Noc2l	1.28
Tfrc	1.278
Gabpb1	1.276
Psmd12	1.274
Cd3eap	1.273
Nampt	1.273
Slc20a1	1.273
Fam102a	1.272
Nip7	1.272
Insr	1.269
Nsfl1c	1.269
Kif1c	1.267
Vcpip1	1.265
Slc16a1	1.264
Nr2c2ap	1.261
Prdx6	1.261
Adam19	1.26
Ncl	1.26
Crot	1.259
Anxa7	1.255
Snx8	1.255
Elovl1	1.253
Fam126a	1.253
Psmc2	1.253
Cndp2	1.252
Tgif2	1.25
Srd5a3	1.249
Adar	1.248
Lsm10	1.248
Srf	1.248
Xkr8	1.247
Eif1	1.246
Psmd3	1.246
Ddx31	1.245
Psmd8	1.245
Rps6ka3	1.245
Rrp15	1.245
Adrm1	1.243
Irgq	1.241
Kdm6b	1.241
Slc7a1	1.24
Csrp1	1.238

Larp1	1.237
Lrrfip2	1.237
Adsl	1.235
Rps19bp1	1.235
Samd11	1.234
Keap1	1.233
Mllt6	1.233
Psmd14	1.233
Spen	1.232
Spata2	1.231
Tgfbr1	1.229
Wasl	1.229
Nmi	1.228
Gapdh	1.227
Hnrnpa0	1.227
Asns	1.226
Hpcal1	1.226
Urb2	1.226
Rbm19	1.225
Thumpd1	1.224
Usp14	1.224
Cebpg	1.221
Nup54	1.221
Pfdn4	1.22
Mthfd1l	1.219
Tmem115	1.219
Cnppd1	1.218
Trappc5	1.218
Ddx21	1.217
Yrdc	1.217
Rrp12	1.216
Pdlim5	1.215
Pgrmc1	1.214
Lactb	1.213
Nutf2	1.213
Vrk2	1.213
Aen	1.212
Chchd5	1.212
Fem1c	1.211
Foxo1	1.211
Dnajc2	1.21
Rab3gap2	1.209
Rangrf	1.209
Psma1	1.208
Irf1	1.207
Ssbp3	1.206
Comt	1.205
Psmd11	1.205

Psmg3	1.205
Gpatch4	1.204
Brd4	1.203
Gars	1.203
Chd7	1.2

Supplemental Video legend.

Supplemental Video 1: Montage of Time lapse intravital tibial bone marrow imaging of GFP+ Vk14451 tumor bearing mice untreated. Tumors are sessile and are not phagocytized by macrophages. Time and scale are marked on individual movies

Supplemental Video 2: Montage of Time lapse intravital tibial bone marrow and spleen imaging of GFP+ Vk14451 tumor bearing mice 4hrs after LCL161 treatment. Examples (highlighted with yellow arrow) of tumors blebbing while in contact with CD169-PE+ macrophages. Also macrophages are seen taking up GFP+ cells and becoming CD169-PE or Texas-Red, GFP double-positive cells. Time and scale are marked on individual movies.

Methods

Western Blot analysis. Total cell lysates were prepared in RIPA buffer in the presence of protease inhibitors. Proteins were separated by SDS-PAGE on 4-12% ready-made gradient gels (Novex) and transferred onto nitrocellulose membranes. After incubation in 5% BSA, blots were stained overnight with anti p100/p52 antibody (18D10, Cell Signaling Technology), incubated with anti-rabbit-IRD680 secondary antibodies (LI-COR Biosciences) and imaged on an Odyssey infra-red imaging system (LI-COR Biosciences).

Cell proliferation assay. 1,500 logarithmically growing human MM cells were plated in quadruplicate in 384 well plates and grown in complete medium in the presence of vehicle, increasing concentration of LCL161, 50ng/ml TNF or the combination. After three days, CellTiter-Glo® reagent (Promega) was added to each well and cell luminescence was measured on a Flexstation (Molecular Devices).

Immunohistochemistry. Tissues were formalin fixed overnight at 4°C, paraffin embedded and processed as previously described¹. After antigen retrieval (microwave in EDTA 1mM pH=7.4), deparaffinized slides were stained overnight with antibody against cleaved caspase 3 (Asp175, Cell Signaling), followed by incubation with pre-absorbed AP-conjugated secondary antibody (Jackson ImmunoResearch). Chromogenic detection was performed by incubation with the AP substrate NBT-BCIP (Vector Laboratories).

SPEP. Mice were periodically bled by tail nicking. Blood was collected into Microtainer tubes (Becton Dickinson), let coagulate at room temperature and spun for 10 minutes at 2,300g. Sera were analyzed on a QuickGel Chamber apparatus using pre-casted QuickGels (Helena Laboratories) according to

manufacturer's instruction. Densitometric analysis was performed using the clinically certified Helena QuickScan 2000 workstation, allowing a precise quantization of the various serum fractions, including the measurements of gamma/albumin ratio.

Murine cell processing. Mice were euthanized by CO₂ inhalation. Single splenic cell suspensions were generated by mechanical disruption between frosted glass slides, collected into 50 ml conical tubes through 40µm nylon mesh filters and centrifuged at 1200 rpm for 5mins. Cell pellets were suspended in ACK cell lysis buffer and immediately centrifuged to remove red cells. After washing in ice-cold saline buffer, cells were counted and viability assessed by trypan blue exclusion.

Purification of CD138⁺ MM cells. CD138-PE (282-1, Biolegend) labeled MM cells from spleen or bone marrow (BM) of tumor bearing mice were magnetically purified using the EasySep™ PE positive selection kit (Stemcell Technologies) according to manufacturer's protocol. Cell purity post selection was determined by flow cytometry and only samples containing >92% CD138⁺B220⁻ cells were utilized for subsequent experiments. Purification of human MM cells has been previously described².

Supplemental references.

1. Chesi, M., *et al.* AID-dependent activation of a MYC transgene induces multiple myeloma in a conditional mouse model of post-germinal center malignancies. *Cancer Cell* **13**, 167-180 (2008).
2. Keats, J.J., *et al.* Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell* **12**, 131-144 (2007).

Supplementary data

Mayo Clinic Cancer Center

Phase II Study of LCL161 Alone and in Combination with Cyclophosphamide in Patients with Relapsed or Refractory Multiple Myeloma.

Study Chairs: P. Leif Bergsagel, MD
Mayo Clinic
13400 E Shea Blvd
Scottsdale, AZ 85259
480/301-8335
480/301-6993 (FAX)

Study Cochairs: Asher Chanan-Khan, MD, Florida
Yi Lin, MD, PhD, Rochester

Statistician: Amylou C. Dueck ✓

Drug Availability

Novartis Supplied Investigational Agents: LCL161

Commercial Agents: Cyclophosphamide

IND # 102,040

✓Study contributor(s) not responsible for patient care.

Document History	<i>May 8, 2013</i> (Effective Date)
Activation	11/07/2013
MCCC Addendum #1	02/16/14
MCCC Addendum #2	November 17, 2014
MCCC Addendum #3	pending

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Craig Nichols, Quality Assurance Specialist Phone: 507-293-1465 E-mail: nichols.craig@mayo.edu
Protocol document, consent form, regulatory issues	Rachel Condjella, Research Protocol Specialist Phone: 480-301-4194 Email: condjellalicerachel@mayo.edu
Adverse Events (paper AdEERS, MedWatch, Non-AER, AML/MDS)	Patricia G. McNamara, SAE C Phone: (507) 266-3028 E-mail: mcnamara.patricia@mayo.edu
Biospecimens	Rochester: Kimberly J. Henderson Phone: (507) 284-3805 Email: henderson.kimberly@mayo.edu Arizona and Florida: Greg Ahmann Phone: (480) 301-4272 Email: Ahmann.gregory@mayo.edu

*No waivers of eligibility per NCI

Index

Schema

- 1.0 Background
- 2.0 Goals
- 3.0 Patient Eligibility
- 4.0 Test Schedule
- 5.0 Grouping Factor
- 6.0 Registration Procedures
- 7.0 Protocol Treatment
- 8.0 Dosage Modification Based on Adverse Events
- 9.0 Ancillary Treatment/Supportive Care
- 10.0 Adverse Event (AE) Reporting and Monitoring
- 11.0 Treatment Evaluation
- 12.0 Descriptive Factors
- 13.0 Treatment/Follow-up Decision at Evaluation of Patient
- 14.0 Body Fluid Biospecimens
- 15.0 Drug Information
- 16.0 Statistical Considerations and Methodology
- 17.0 Pathology Considerations/Tissue Biospecimens
- 18.0 Records and Data Collection Procedures
- 19.0 Budget
- 20.0 References

Consent Form

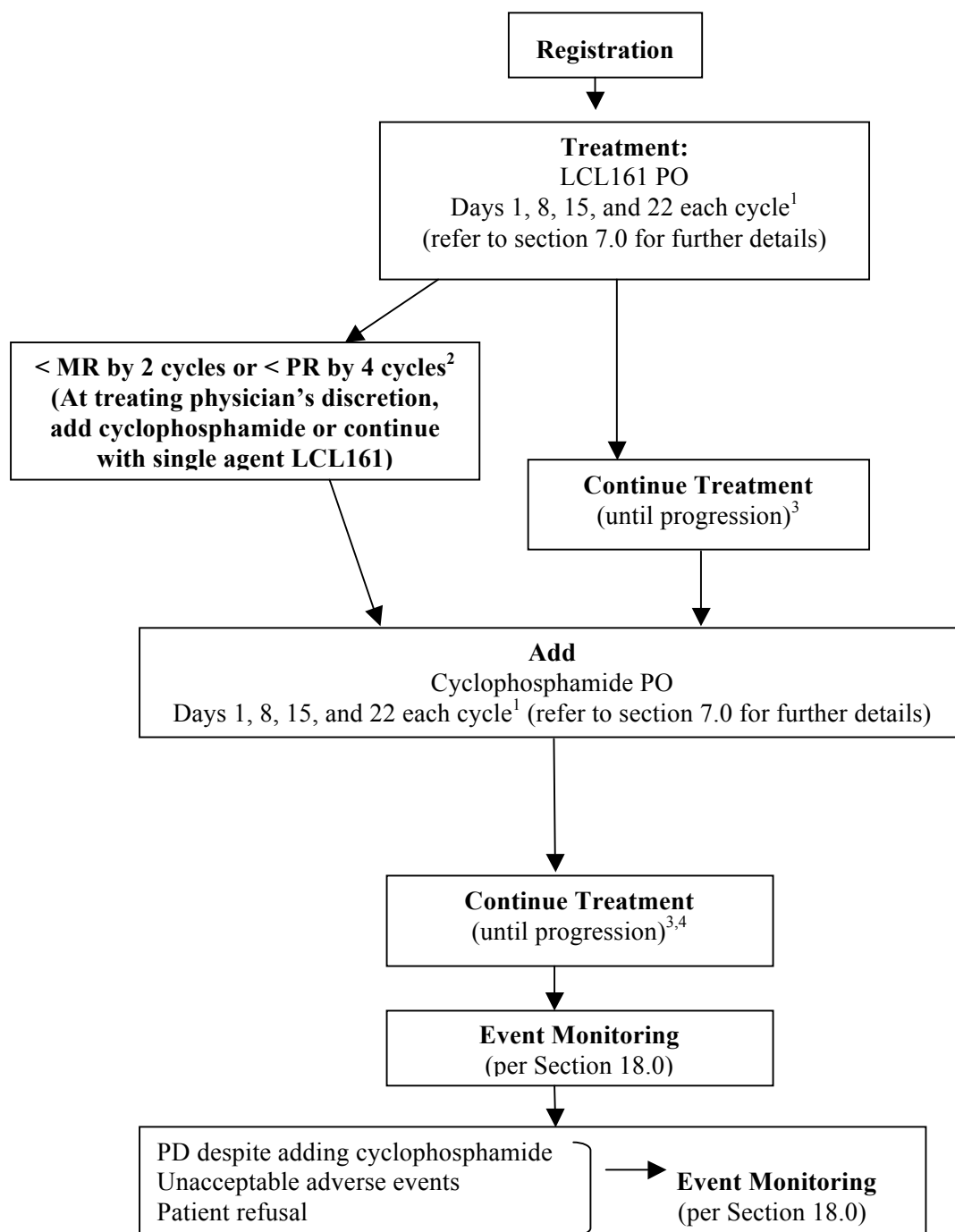
Appendix I - ECOG Performance Status

Appendix II – Mayo Risk Stratification

Appendix III - Concomitant Medications Guidance

Appendix IV - Patient Medication Diary

Appendix V – Patient Information Sheet and Linear Analog Self-Assessment (LASA)

Schema

1 Cycle length = 28 days

2 MR by 2 cycles and PR by 4 cycles can be unconfirmed responses

3 Confirmation of PD is not required

4 When adding Cyclophosphamide, new baseline disease measurement will be established (see Section 7.11). Cyclophosphamide will be discontinued after 12 cycles of administration.

Generic name: LCL161	Generic name: Cyclophosphamide
Brand name(s): None	Brand name(s): Cytosan, Neosar
Mayo Abbreviation: LCL161	Mayo Abbreviation: CTX
Availability: Provided by Novartis	Availability: Commercially

1.0 Background

1.1 Multiple Myeloma

1.11 Multiple myeloma (MM) is a plasma cell malignancy characterized by bone destruction, anemia, hypercalcemia, and renal failure that affects about 16,000 individuals and results in nearly 12,000 deaths in the United States each year. Multiple Myeloma is characterized by accumulation of malignant plasma cells primarily in the bone marrow, with malignant cells seen in the peripheral blood in significant numbers only in the late disease stages. Clinically myeloma is characterized by destructive bone lesions, renal insufficiency, anemia, and or hypercalcemia. The bone lesions can be especially painful and contributes to the significant morbidity seen with myeloma. Destructive lesions of the vertebral bodies can result in spinal cord compromise and serious neurological consequences. Renal failure in myeloma also contributes to significant morbidity and can be the result of light chain cast nephropathy or a consequence of hypercalcemia or hyperuricemia. Median survival with conventional dose melphalan and prednisone is 3-4 years, which has not been significantly improved by the addition of other chemotherapeutic agents. High dose therapy and autologous stem cell transplantation improves the survival compared to conventional therapy, but is not curative with almost all patients eventually relapsing from their disease. While allogeneic stem cell transplant can be potentially curative, it is associated with significant treatment related mortality as well as morbidity secondary to graft versus host disease. Introduction of thalidomide and its immunomodulatory derivatives such as lenalidomide as well as the proteasome inhibitor bortezomib has opened up more options for patients with relapsed disease and has resulted in increased response rates when applied to patients with newly diagnosed myeloma. Rationally designed therapies based on a thorough understanding of the disease mechanisms remain the need of the hour. It is important that developmental therapeutics in myeloma, as is any malignancy, need to be focused on developing novel agents that can target biological pathways or events critical to disease initiation and progression.

1.12 Rationale for Study - Although the median survival has increased from 3 years to more then 6 years over the last decade, the majority of patients with multiple myeloma continue to die from their disease. Patients who have been treated with an alkylating agent, glucocorticoids, immunomodulatory drug of the IMiD[®] class (thalidomide, lenalidomide, pomalidomide) and a proteasome inhibitor (bortezomib, carfilzomib) have few remaining treatment options. Although patients may respond to retreatment with different drugs within these classes, the duration of response is generally of short duration. Once patients have become refractory to both IMiDs and proteasome inhibitors, the median survival is only 9 months (Kumar, et al, 2012). There is clearly a need for better treatment options for these patients.

- 1.13 Although different kinds of alkylators, glucocorticoids and proteasome inhibitors are used in the treatment of MM, there is essentially only a single class of immunomodulatory drug, all based on the backbone of thalidomide. Unfortunately the mechanism of actions of IMiDs is poorly understood. They have essentially no anti-tumor activity *in vitro*, or in xenograft models, and the clinical activity was discovered empirically. Their teratogenic activity, and whatever little direct *in vitro* anti-tumor activity they possess requires interaction with cereblon, part of an E3-ubiquitin ligase complex (Zhu, et al, 2011). They have a pleiotropic mechanism action, with the best characterized being immune modulation. Although they were initially selected by their ability to inhibit TNF α secretion by LPS-stimulated monocytes, in patients they result in increased levels of TNF α , IL8 and other inflammatory cytokines in the serum, and increased numbers and activation of NK cells (Chanan-Khan, et al, 2011).

1.2 Overview of LCL161

LCL161 is a biostable, cell permeable, small molecular weight SMAC mimetic compound that binds with high affinity to cIAP1 (and likely cIAP2), and to a tenfold lesser extent, XIAP. The binding leads to the degradation of cIAP1, part of an E3-ubiquitin ligase complex that regulates the stability of NIK, and activation of the non-canonical NF κ B pathway (Vallabhapurapu, et al, 2008). LCL161 treatment of cell lines results in a pulse of NF- κ B activity and cytokine release. This effect of LCL161 may underlie the efficacy of LCL161 in some tumor models and also the dose-limiting toxicity of cytokine release syndrome observed in some patients treated with the highest doses of LCL161. We noted that the NF κ B pathway is frequently activated by a promiscuous array of mutations in MM, including biallelic deletion of cIAP1/2 (Keats, et al, 2007). This suggests that LCL161 will have little direct anti-tumor activity in MM, but may in fact result in some increase in the already high level of NF κ B. However this pathway is also a key regulator of the host immune response so that LCL161 induces a general activation of the immune system, particularly innate immunity.

Like IMiDs, LCL161 has little direct anti-tumor activity against primary MM cells, MM cell lines, or in xenograft models. However it has dramatic activity against MM that develops spontaneously in an immunocompetent genetically engineered V κ *MYC mouse model of MM (Figure 1). Notably, it has no activity *in vitro* against these same tumor cells, suggesting an important role for the host in mediating the anti-tumor

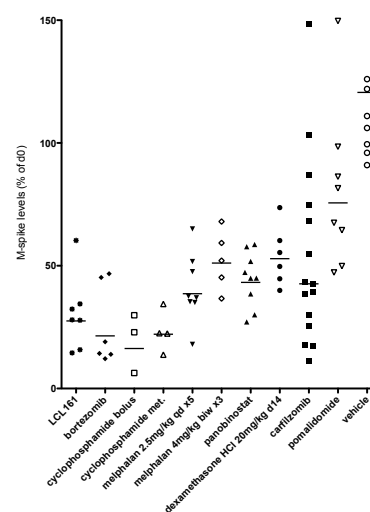


Figure 1. LCL-161 is highly active in an immuno-competent mouse model of MM. Mice with MM were treated with the indicated drugs and the change in the M-spike at d14 plotted.

effect. The Vk*MYC model has been rigorously validated and found to have a positive predictive value for clinical activity of 67%, and a negative predictive value for clinical inactivity of 88%⁶. Given the importance of immunodulatory drugs in the treatment of patients with MM, and the clear pre-clinical evidence of marked anti-tumor immunodulatory activity of LCL161, there is a strong rationale for evaluating its activity in MM patients.

Drugs used in the treatment of multiple myeloma have profound effects on the immune system. Dexamethasone and bortezomib (which inhibits NFkB) are profound immunosuppressants. IMiDs in general activate the immune system. There is a large body of literature that metronomic cyclophosphamide has profound immunodulatory activity, reducing suppressor T regulatory cells, resulting in an activation of the immune system, with improved responses to vaccines and other immune therapies. Interestingly, we observe in combination studies in Vk*MYC mice with MM that addition of either dexamethasone or bortezomib antagonizes LCL161, while this effect is not seen with either cyclophosphamide or pomalidomide (Figure 2).

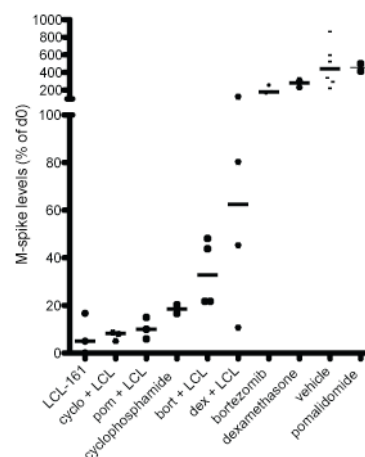


Figure 2. Bortezomib and dexamethasone antagonize LCL161 activity in VkMYC MM. Vk12598 engrafted mice received the indicated drugs. The M-spike levels after two weeks of treatment were normalized to the level at d0.

1.21 Preclinical experience

In vitro pharmacology

LCL161 binds with high affinity to, cIAP1, and cIAP2 (and to a lesser extent XIAP) through their BIR3 domains. LCL161 binding to cIAP1 causes cIAP1 autoubiquitination and degradation of cIAP1 by the proteasome in a dose-dependent manner. Loss of cIAP1 occurs rapidly (within 30 minutes) in both sensitive and insensitive cell lines. Since this phenomenon is also observed in human PBMCs, the measurement of cIAP1 protein levels is a useful pharmacodynamic biomarker.

1.22 Nonclinical pharmacokinetics and drug metabolism

The pharmacokinetics of LCL161 was investigated in the rat, dog, and monkey. LCL161 is rapidly and extensively absorbed in all animal species tested after an oral dose. The compound has a low to moderate plasma clearance and a moderate to high volume of distribution at steady state, indicating wide tissue distribution. LCL161 is highly bound to plasma protein across all species examined with saturable plasma protein binding at high concentrations. Results from the rat ADME study demonstrated that [¹⁴C]LCL161 is mainly excreted into feces, with minor renal excretion (~21%), and this was confirmed in orally dosed, bile duct

cannulated animals. The major metabolic pathway for LCL161 based on *in vitro* studies in human hepatocytes involves cytosolic NADPH-dependent carbonyl reductase(s) (~60%), while a minor pathway exists for oxidative metabolism (~40%) by CYP2C8 and by CYP3A4. No unique, major metabolites were identified in human hepatocytes. LCL161 is a P-glycoprotein (P-gp) substrate, which may affect the distribution of LCL161 to tissues expressing this efflux transporter (e.g., brain).

With respect to potential drug-drug interactions (DDI), *in vitro* data suggested that there is a high risk for clinically relevant CYP3A4/5 time-dependent inhibition ($K_i \sim 0.8 \mu\text{M}$) and a clinical DDI drug-drug interaction study with midazolam (CLCL161A2105) confirmed this finding *in vivo*. LCL161 is also a reversible CYP2B6 inhibitor ($K_i \sim 0.2 \mu\text{M}$) based on *in vitro* data; the clinical relevance has not been confirmed *in vivo*.

1.23 Nonclinical toxicology

Safety pharmacology studies demonstrated that LCL161 had no significant effects on the function of the central nervous system (CNS), cardiovascular and respiratory systems. It is also considered non-genotoxic, as shown by the results of *in vitro* genetic toxicology studies. In the general toxicology studies, LCL161 was administered to rats and monkeys by oral (gavage) for up to 4-weeks with once daily dosing. The doses for the 4-week rat study were: 0 (control), 3, 10 and 20 mg/kg/day, and the doses for the 4-week monkey study were 0 (control), 10, 30 and 45 mg/kg/day. The following are considered the main target organs of toxicity: lymphoid hyperplasia and general inflammation in both rats and monkeys and bone/joint lesions in rats only. The STD_{10} in the rat was determined to be 10 mg/kg/day, with steady-state systemic exposure ($\text{AUC}_{0-24\text{h}}$) of 19,800 ng.hr/mL (males and females combined), and the highest non-severely toxic dose (HNSTD) in monkeys was 30 mg/kg (360 mg/m², males and females combined).

General inflammation was the most prominent finding in the daily dosed toxicology studies. In rats, inflammatory changes were observed in mesenteric and mandibular lymph nodes, the spleen, the skin, bone/joints, bone marrow, serosa/adventitia of thoracic, abdominal and subcutaneous organs/tissues, lungs, gastrointestinal (GI) tract and liver. In general, the lesions were dose dependent and fully reversed, or showed a tendency towards reversibility upon drug withdrawal. Clinical pathology changes in rats were also indicative of inflammation, including decreases in lymphocytes and eosinophils, increases in neutrophils and monocytes, and abnormal neutrophil and lymphocyte morphology. In monkeys, evidence of inflammation was observed in the kidney, liver, lacrimal gland, salivary gland, lungs and stomach. The inflammation in the monkeys was reversed after a 4-week recovery period. Clinical pathology changes were also indicative of inflammation, including increases in peripheral leukocyte counts, increased fibrinogen and C-

reactive proteins, and increased bone marrow myeloid: erythroid ratios, although the degree of clinical pathology findings was generally minor. Cytokine analysis identified sporadic increases in serum concentrations of IL-1 beta, IL-2, IL-6, TNF- α , and GM-CSF.

General inflammation is believed to be related to LCL161's mechanism of action. Inhibition of IAPs leads to activation of the NF- κ B pathway and to the increased production of inflammatory cytokines such as TNF- α in tumors. While TNF- α has not been demonstrated to be responsible for the inflammation observed in animals, other cytokines including GRO-KC (a rat-specific analog of IL-8) and MCP-1 have been characterized. Based on the understanding of the mechanism of action and on preclinical data, the inflammation is reversible upon discontinuation of drug.

Based on the dose limiting toxicity for LCL161 of generalized inflammation, it was of interest to evaluate the impact on the *in vivo* safety profile of combining LCL161 with an anti-inflammatory corticosteroid. Dexamethasone, selected as the corticosteroid due to its common use in rodents, was assessed in three contexts. First, 0.3 mg/kg/day of dexamethasone (modeled from 20 mg of dexamethasone in humans daily) was administered to rats prior to LCL161 and in combination with each LCL161 dose over a 2-week period. In this study, steroids in combination with LCL161 were able to prevent the majority of the inflammatory findings. In a second experiment, dexamethasone dosing was not started until LCL161-mediated inflammation had been allowed to fully develop in rats, and it was then given at 0.1 mg/kg daily for 5 days (modeled from 40 mg of prednisone in humans daily). In this context, dexamethasone suppressed the inflammation and bone changes. A 5-day drug holiday without the administration of dexamethasone also diminished inflammation and bone changes significantly, but not to the same degree as treatment with dexamethasone. In a third experiment designed to test whether treatment with dexamethasone impaired tumor killing, dexamethasone at 0.5 mg/kg/week was administered as a pre-dose (modeled from 3 mg dexamethasone in humans as a pre-dose) with 150 mg/kg of LCL161 given weekly to tumor-bearing mice (MDA-231 xenograft). In this study, steroids did not antagonize the anti-tumor activity of LCL161 (see Investigator's Brochure).

Lymphoid hyperplasia is consistently observed in animal studies with daily doses. In rats and monkeys, enlarged spleen and lymph nodes and microscopic evidence of lymphoid hyperplasia was observed. The spleen appears to be the most sensitive organ for LCL161 induced lymphoid proliferative changes, and lymphoid hyperplasia was observed in spleen at all doses in the rat and monkey 4-week GLP studies. Hyperplastic changes of lymph nodes were also observed in multiple organs/tissues in rat and monkeys - often at higher doses. Lymphoid hyperplasia in spleen and lymph nodes were at least partially reversible in the 4-week studies, though 4 weeks may not be long enough for complete recovery for lymphoid hyperplasia.

Effects on bone/joints were observed in toxicology studies with daily dosing in rats, but not in monkeys. The findings include: mesenchymal proliferation, outgrowth of mesenchymal tissues with destruction of cortical bone, periosteal proliferation, new bone formation, decrease in trabecular bone, growth plate thickening and/or disorganization of trabecular bone adjacent to growth plate. Articular findings include inflammation, fibroplasias, and/or necrosis of periarticular soft tissue and exudation in the articular cavity. The findings were dose-dependent. The bone findings were partially reversed during recovery, though it is unlikely that a 4- to 6-week recovery period is long enough for bone findings. It is not certain if the bone/joint findings are secondary to inflammation, or a direct effect, or both. It is suspected that the bone findings in rats are confounded by the continued presence of open epiphyses and high bone turn over rates. However, due to the lower exposures obtained in the monkey toxicology studies, these bone findings cannot be characterized as species-specific. Final data from the ongoing first-in-human trial suggest that LCL161 does not have clinically significant effects on bone turn over (see Investigator's Brochure).

1.24 Biomarkers

Preclinical and clinical biomarker data from the first-in-human trial (CLCL161A2101) with LCL161 given as a single agent on a once-weekly schedule were used to select the biomarkers employed in this trial to explore the relationship between pharmacokinetics/pharmacodynamics, efficacy, target modulation, molecular response, and immune modulation. Preclinical studies in MDA-MB-231 breast cancer cells treated with LCL161 *in vitro* demonstrated that cIAP1 is degraded within 30 minutes of drug treatment. In mouse studies, maximal degradation of cIAP1 in MDA-MB-231 tumor tissue occurred approximately 6 hrs following PO administration of LCL161. Analysis of clinical data from the CLCL161A2101 trial suggest that cIAP1 is degraded in PBMCs within 2 hrs of LCL161 dosing, and variably recovers around 72 hrs after dosing.

Preclinical studies have demonstrated that the degradation of cIAP1 leads to the transient activation of NF- κ B. They have also shown that NF- κ B activation plus antigen stimulation activates immune cells and stimulates the release of numerous cytokines into the circulation. These effects of LCL161 could underlie the inflammation observed with chronic dosing in rats and monkeys and the cytokine release syndrome observed in patients, described below.

1.25 Human clinical experience

Two clinical trials with LCL161 have been completed and final data are available (Investigator's Brochure). Two clinical trials with LCL161 are ongoing.

1.251 CLCL161A2101, a first-in-human clinical trial

CLCL161A2101 was a phase 1 dose escalation study designed to identify the maximum tolerated dose (MTD), safety and tolerability of LCL161 when given as a single oral dose once each week, and to seek preliminary evidence of activity.

A total of 53 patients with advanced solid tumors (relapsed or refractory) were enrolled, and patients received oral LCL161 on Days 1, 8, and 15 of every 21-day cycle at doses ranging from 10-3000 mg.

Clinical safety and tolerability

The most common adverse events of any CTCAE grade observed that were suspected to be related to LCL161 included fatigue, nausea and vomiting. In general these toxicities were manageable and severe toxicity was unusual. Eight patients (15%) experienced grade 3 or 4 toxicities that were considered to be related to LCL161. Three patients (5.6%) experienced DLTs (one each at doses of 1800 mg, 2100 mg and 3000mg). All DLTs were a clinical syndrome of cytokine release (CRS) that is consistent with the mechanism of action of LCL161 and that variably included vomiting, diarrhea, fever, flushing or pruritic rash, and in the most severe cases symptomatic hypotension. Symptoms occurred on the day of dosing within hours of having received LCL161. Two patients experienced grade 3 CRS (one each at 1800 and 2100 mg), both of whom recovered within 24 hours of the development of symptoms. One patient (at 3000 mg) developed significant hypotension with grade 4 cytokine release syndrome. The severe hypotension experienced by this patient was unusual and may have been complicated by concomitant administration of three anti-hypertensive medications including amlodipine, which is metabolized by CYP3A4. In the 1800 mg dose group one patient (4%) among 24 developed grade 3 CRS as a DLT; this dose was selected as the dose recommended for further study.

Laboratory abnormalities including hematological toxicity was uncommon. The most common severe hematological abnormality was lymphopenia, which occurred in 8 patients (15%), followed by anemia in 5 patients (9%) and grade 4 thrombocytopenia in 1 patient (1.8%). No severe or life threatening hematologic abnormalities were reported for WBC or absolute neutrophils (neutropenia). Neuropathy or pneumonitis were not reported as new adverse event.

Clinical pharmacokinetics

LCL161 was rapidly absorbed after a single oral dose of a tablet formulation, with peak plasma concentrations occurring between 1.0 and 6.2 hours. LCL161 exhibited variable PK, with a large apparent volume of distribution (V_z/F) ranging from 190-1689 L, a moderate apparent total body clearance (CL/F) ranging from 13-151 L/h, and a terminal elimination half-life ($T_{1/2}$) ranging

from 4.4-15.5 hours. LCL161 C_{max} and AUC_{inf} generally increased with increasing doses; however, a slightly less than proportional increase was observed. Substantial inter-patient variability was observed in LCL161 PK at the RDE of 1800 mg with the percent coefficient of variation of 78% for C_{max} and 84% for AUC(0-inf). There was no accumulation in LCL161 plasma C_{max} or AUC(0-6) from Day 1 to Day 8 and no evidence for time-dependent effects on PK following weekly oral administration of LCL161.

Clinical pharmacodynamics

This study provided evidence that LCL161 is pharmacodynamically active at tolerable doses investigated in patients. The principal marker of pharmacodynamic activity was degradation of cIAP1. Target degradation was observed in all paired tumor biopsies obtained prior to and following a single dose of LCL161, including one case at 900 mg and five cases at 1800 mg. cIAP1 degradation was also observed in some paired skin biopsies at doses ≤ 160 mg and in 22 of 24 the samples at doses ≥ 320 mg. cIAP1 depletion in skin was consistently evident 24 hours after LCL161 dosing. The evidence of pharmacodynamic activity (cIAP1 degradation) at doses ≥ 320 mg suggests that 1800 mg, the dose chosen for further study, is well above that required for target inhibition. The time course of degradation and recovery of cIAP1 protein levels after a single weekly dose of LCL161 was characterized in PBMCs. The data demonstrated that cIAP1 is rapidly degraded within 2 hours of treatment with LCL161 and suggested that protein levels begin to recover in most patients approximately 72 hours after dosing.

Clinical efficacy

No evidence of anti-tumor activity was identified in this unselected population, which is consistent with the preclinical data that suggest a small proportion of malignant cell lines are sensitive to LCL161 as a single agent.

For more information, refer to the [Investigator's Brochure].

1.252 CLCL161A2105, a drug-drug interaction study with midazolam

To evaluate the clinical risk of CYP3A4/5 inhibition by LCL161, the clinical drug-drug interaction (DDI) study CLCL161A2105 was conducted in 16 healthy patients. This study evaluated the effect of a single 600 mg dose of LCL161 on the PK of the sensitive CYP3A probe substrate, midazolam. The study was also designed to evaluate the time-course of CYP3A4/5 recovery with repeat, single oral doses of midazolam (2 mg) given 3 and 7 days after LCL161. This study had no accompanying pharmacodynamic or efficacy endpoints.

Clinical safety and tolerability

Among the 16 healthy patients treated with LCL161 and midazolam, one patient developed possible grade 1 CRS characterized by transient fever and neutrophilia approximately 12 hours after dosing.

Clinical pharmacokinetics

LCL161 exhibited rapid absorption in healthy patients with a T_{max} ranging from 1.0-4.0 hours and a T_{1/2} ranging from 4.5-7.6 hours. A strong drug interaction was observed when LCL161 and midazolam were dosed on the same day: midazolam C_{max} was increased 3-fold and AUC(0-inf) was increased 9-fold. The drug interaction was transient, however. CYP3A4/5 enzyme activity was greater 3 days after the single dose of LCL161 compared to baseline, with midazolam C_{max} and AUC(0-inf) decreased by approximately 30%. Enzyme activity completely returned to baseline levels within 7 days of dosing.

Based upon the preclinical and clinical data from this DDI study, caution should be used for patients receiving LCL161 who are taking medications that are substrates for CYP3A4/5.

For more information, refer to the [Investigator's Brochure].

1.253 CLCL161A2104: A combination study with weekly paclitaxel

CLCL161A2104 is an ongoing phase Ib dose-escalation study of LCL161 with paclitaxel in which patients are treated with a fixed, standard dose of paclitaxel (80 mg/m² IV once weekly) followed immediately by oral LCL161 once weekly at doses ranging from 600 mg to the RDE (recommended dose for expansion) of 1800 mg. The objectives of the study are to define the MTD, safety, tolerability, pharmacokinetics and pharmacodynamics of LCL161 in combination with paclitaxel. Eligible patients are aged ≥18 years, with advanced solid tumors that have progressed despite the use of standard therapies or for which no effective therapies are available.

Clinical safety and tolerability

As of July 31st, 2012, preliminary AE data are available from 52 patients receiving treatment with LCL161 + paclitaxel; 600 mg LCL161 (n=3), 1200 mg LCL161 (n=5), 1500 mg LCL161 (n=5), and 1800 mg LCL161 (n=39). The most common AE regardless of relationship to LCL161 is anemia of any grade, occurring in 32 out of 52 (62%) patients. Other common AEs (greater than 10%) include diarrhea (58%); asthenia and nausea (48%); neutropenia (44%); pyrexia (37%); fatigue (33%); alopecia and constipation (31%); decreased appetite (29%); vomiting (25%); mucosal inflammation (23%); dyspnea, rash, and peripheral neuropathy (21%); abdominal pain (19%);

dysgeusia (17%); peripheral oedema (15%); cough, dyspepsia, myalgia, peripheral sensory neuropathy, urinary tract infection (13%); dizziness, febrile neutropenia, headache, neutrophil count decreased, pruritus, and respiratory tract infection (12%).

Neutropenia was the most common Grade 3 and Grade 4 adverse event (17% and 19% respectively). Ten of the 52 (19%) patients experienced Grade 3 anemia; no Grade 4 anemia was reported.

Two patients (600 mg and 1800 mg) experienced a Grade 1 CRS. The incidence and severity of CRS is lower than that observed in patients treated with LCL161 as a single agent. This is consistent with the preclinical and extensive clinical experience with dexamethasone as a suppressant of cytokine release and inflammation. Dexamethasone is given to all patients on the CLCL161A2104 study as a premedication to prevent hypersensitivity reactions to paclitaxel.

As of August 10th, 2012, 28 patients (54%) experienced SAEs. Three cases were suspected to be related to treatment with LCL161, including two cases of non-infectious pneumonitis and one case of asymptomatic ALT elevation; all three recovered fully. No deaths have occurred that were considered related to LCL161.

Overall, five patients have developed non-infectious pneumonitis among 55 patients evaluable for this toxicity. Three patients experienced grade 3 pneumonitis and two patients experienced grade 2 pneumonitis; two patients experienced pneumonitis as a serious adverse event. One patient with grade 3 pneumonitis had twice received palliative radiation to the chest wall, most recently ten weeks prior to treatment with paclitaxel and LCL161. This patient developed radiation pneumonitis in the radiation field as an SAE. All cases have occurred at a single geographic location at which 25 of the 55 patients have been treated. All five patients responded promptly to treatment with corticosteroids and recovered fully. Of the three initial cases reported, two were rechallenged with LCL161 and paclitaxel. Both patients weaned off corticosteroids and remain on treatment. After at least six additional cycles of study treatment each, neither patient has had a recurrence of pneumonitis. The third patient withdrew consent. Pneumonitis did not occur as a toxicity of LCL161 as a single agent on the CLCL161A2101 study. Radiation pneumonitis as a toxicity of paclitaxel is listed on the drug label; nonetheless the incidence of pneumonitis observed in this study is higher than expected.

Clinical pharmacokinetics

Preliminary noncompartmental PK analysis was conducted on patients with full PK sampling. LCL161 C_{max} and AUC_{inf} did not increase with increasing doses from 600 to 1800 mg. The lack of increase in exposure with increasing LCL161 doses is

consistent with the first-in-human study where dose proportionality could not be definitively claimed due to the small sample sizes and the large inter-patient variability. Based on preliminary analysis, co-administration of paclitaxel and LCL161 does not appear to result in a PK interaction. At the 1800 mg dose level, the median LCL161 C_{max} and AUC_{inf} were comparable to values observed following single agent LCL161. Paclitaxel plasma PK parameters were unaffected by increasing doses of LCL161 and were consistent with published data for weekly paclitaxel dosed at 80 mg/m² as a 1 hour infusion (Campone et al 2009; Ready et al 2007), indicating LC:161 has no effect on the PK of paclitaxel.

Clinical efficacy

Among the 45 patients, 11 have confirmed PRs to study treatment.

For more information, refer to the Investigator's Brochure.

1.254 CLCL161A2201: neoadjuvant, randomized weekly paclitaxel with or without LCL161

CLCL161A2201 is an ongoing phase II open-label, neoadjuvant, randomized study of weekly paclitaxel with or without LCL161 in patients with triple negative breast cancer. Following a screening period to determine eligibility, patients are randomized to either paclitaxel 80 mg/m² IV given weekly (the control arm) or paclitaxel 80 mg/m² IV weekly immediately followed by LCL161 1800 mg PO once weekly (the experimental arm). Treatment will be administered each week for 12 weeks (4 cycles). The length of each treatment cycle is 21 days. The objectives of this trial are to assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with triple negative breast cancer that are positive for a gene expression signature being tested for its ability to identify tumors more likely to benefit from treatment with LCL161 + paclitaxel.

1.255 Potential for drug-drug interactions

The risk for clinically significant DDI with the proposed combination of LCL161 and CP is considered to be moderate. LCL161 is a potent time-dependent inhibitor of CYP3A4/5 based on in vitro studies and based on a DDI study with midazolam in healthy subjects. In vitro studies also indicate LCL161 is a reversible CYP2B6 inhibitor. Cyclophosphamide (CP) is a prodrug that requires bioactivation via cytochrome P450 enzymes (mainly CYP2B6) to form 4-OHCP (de Jonge et al., 2005, Chang et al., 1993, Huitema et al., 2000). 4-OHCP is unstable and rapidly converts to phosphoramidate mustard (PM), the active DNA alkylating agent. Inactivation routes are mediated by CYP3A4 to form 2-dechloroethylcyclophosphamide and by aldehyde dehydrogenases. Inhibition of CYP2B6 and

CYP3A4/5 by LCL161 could affect efficacy and toxicity of CP. Several examples from the literature demonstrate that inhibition of CYP2B6 can inhibit bioactivation of CP (Huitema et al., 2000) or inhibition of CYP3A4/5 can decrease exposure of 4-OHCP (Marr et al., 2004, Mollgard et al., 2005). Therefore, it is possible that co-administration of LCL161 and CP could affect the efficacy or toxicity of CP.

Conversely, CP is not likely to significantly alter exposure to LCL161. The major metabolic pathway for LCL161 based on in vitro studies in human liver involves cytosolic NADPH-dependent carbonyl reductase(s), with minor contributions from oxidative metabolism by CYP2C8 and CYP3A4/5. LCL161 is a substrate for P-gp and could potentially be affected by inhibitors or inducers of P-gp transporters. CP has not been reported to interact with the enzymes and transporters involved in LCL161 drug disposition.

1.3 Overview of cyclophosphamide

Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA. Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug.

Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%. It has not been demonstrated that any single metabolite is responsible for either the therapeutic or toxic effects of cyclophosphamide. Although elevated levels of metabolites of cyclophosphamide have been observed in patients with renal failure, increased clinical toxicity in such patients has not been demonstrated.

2.0 Goals

2.1 Primary

2.11 To evaluate the confirmed overall response rate (\geq PR) to LCL161, used as a single agent, in patients with relapsed MM

2.2 Secondary

- 2.21 To estimate the confirmed overall response rate to LCL161 in combination with cyclophosphamide, when cyclophosphamide is added to LCL161 for lack of response or progression
- 2.22 To estimate the overall survival and event-free survival of patients treated with LCL161 in combination with cyclophosphamide, when cyclophosphamide is added to LCL161 for lack of response or progression
- 2.23 To evaluate the tolerability of LCL161 alone and in combination with cyclophosphamide in patients with relapsed MM
- 2.3 Correlative Research
 - 2.31 To determine degradation of cIAP1 in PBMC, changes in serum cytokines, and changes in immune cell subsets by flow cytometry
 - 2.32 To correlate the effect of LCL161 with the presence of activating mutations of the NFkB pathway
 - 2.33 To evaluate the PK of LCL161 alone, and LCL161 in combination with cyclophosphamide
 - 2.34 To describe patient-reported health-related quality of life and symptoms

3.0 Patient Eligibility

- 3.1 Inclusion Criteria
 - 3.11 Relapsed or refractory multiple myeloma and has already received ≤ 4 standard treatment regimens. Note: Induction, transplant, consolidation, and maintenance is considered one regimen.
 - 3.12 Age ≥ 18 years
 - 3.13 Have received prior therapy with an immunomodulatory agent, a proteasome inhibitor, and glucocorticoids.
 - 3.14 The following laboratory values obtained ≤ 14 days prior to registration.
 - Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$
 - Untransfused platelet count $\geq 75,000/\mu\text{L}$
 - AST $\leq 3\times$ ULN
 - ALT $\leq 3\times$ ULN
 - Total Bilirubin ≤ 1.5 mg/dL
 - Serum Creatinine ≤ 2.5 mg/dL
 - Hemoglobin ≥ 8 g/dL
 - 3.15 Measurable disease of multiple myeloma as defined by at least ONE of the following:

- Serum monoclonal protein ≥ 1.0 g/dL (see Section 11.1 for definition)
 - ≥ 200 mg of monoclonal protein in the urine on 24 hour electrophoresis
 - Serum immunoglobulin free light chain ≥ 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
 - Monoclonal plasmacytosis $\geq 30\%$ (evaluable disease).
 - Measurable plasmacytoma that has not been radiated.
- 3.16 ECOG performance status (PS) 0, 1, 2 (Appendix I)
- 3.17 Willing and able to comply with scheduled visits, treatment plan and laboratory tests
- 3.18 Able to swallow and retain oral medication
- 3.19a Provide informed written consent.
- 3.19b Negative serum pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
- 3.19c Willing to provide all biological specimens as required by the protocol for correlative research purposes (see Sections 6.2, and 14.1)
- 3.19d Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).
- 3.19e Mayo Clinic Arizona Only: Willing to participate in associated biobanking study, 919-04. The patient must sign consent to enroll onto the mandatory companion biobanking study in order to participate in this treatment study.
- 3.19f Mayo Clinic Rochester and Florida only: Willing to participate in associated biobanking study, 521-93. The patient must sign consent to enroll onto the mandatory companion biobanking study in order to participate in this treatment study.
- 3.2 Exclusion Criteria
- 3.21 Prior use of investigational drugs ≤ 14 days prior to registration.
- 3.22 Prior use of growth factors ≤ 14 days prior to registration.
- 3.23 Prior radiation therapy ≤ 14 days prior to registration.
- 3.24 Prior autologous stem cell transplant ≤ 12 weeks prior to registration.
- 3.25 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Women of childbearing potential who are unwilling to employ adequate contraception while receiving treatment on this study and for 4 months after stopping treatment on this study
- Men who are unwilling to use a condom (even if they have undergone a prior vasectomy) while having intercourse with any woman, while receiving treatment on this study and for 4 months after stopping treatment on this study.

NOTE: Postmenopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, a woman is considered to be of not child bearing potential only when her reproductive status has been confirmed by follow-up hormone level assessment.

- 3.26 Prior allogeneic transplant of any kind.
- 3.27 Known active infection requiring parenteral or oral anti-infective treatment.
- 3.28 Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse follow-up evaluation.
- 3.29a Known HIV or active hepatitis B or C viral infection.
- 3.29b Active autoimmune/inflammatory conditions requiring ongoing immunosuppressive therapy.
- 3.29c Use of more than low dose corticosteroids (e.g., prednisone up to but no more than 10 mg p.o. q.d. or its equivalent) for symptom management and comorbid conditions, except for the following:
 - Topical applications (e.g. rash),
 - Inhaled sprays (e.g. obstructive airways diseases)
 - Eye drops or local injections (e.g. intra-articular)
 - Joint injections (e.g. arthritis)

Doses of corticosteroid should be stable for at least 7 days prior to registration.

- 3.29d Any concurrent severe and/or uncontrolled medical conditions that could increase the patient's risk for toxicity while in the study or that could confound discrimination between disease- and study treatment-related toxicities.

- 3.29e Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
- History or presence of ventricular tachyarrhythmia
 - Presence of unstable atrial fibrillation (ventricular response > 100 bpm) [**NOTE:** Patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria]
 - Clinically significant resting bradycardia (< 50 bpm)
 - Angina pectoris or acute myocardial infarction ≤ 3 months prior to registration
 - Other clinically significant heart disease (e.g., symptomatic congestive heart failure; uncontrolled arrhythmia or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen)
- 3.29f Currently receiving treatment with agents that are metabolized solely through CYP3A4/5 and have a narrow therapeutic index or are strong CYP2C8 inhibitors; or are receiving treatment with agents that carry a risk for QT prolongation and are CYP3A substrates (see Appendix III, Table 1 for detailed list of prohibited medications). Caution should be used in patients taking other CYP2C8- or CYP3A4/5-interacting agents (see Appendix III, Table 2).
- 3.29g Impaired GI function or GI disease that may significantly alter the absorption of LCL161.

4.0 Test Schedule¹

Cycle = 28 days	Days Prior to Registration		Active Treatment						End of study ¹⁸
	≤30 days	≤14 days	Day 1 of Cycles 1 and 2	Day 8, 15, and 22 Cycle 1	Cycle N ²⁰ day 14 (+/-3 days)	Cycle N ²⁰ Day 9 OR Day 16 OR Day 23	Every cycle, pre-treatment (Cycles 2-6)	Every cycle, pre-treatment (Cycle 7 and thereafter) ¹³	
Complete medical history	X								
Adverse Event monitoring		X	X ⁶	X ^{6, 23}			X ²³	X ²³	X ¹⁸
Physical exam, including weight		X					X ¹⁰	X ¹⁰	
Vital signs		X ¹⁶	X ¹⁷				X	X ¹⁰	
Height		X							
Performance status (ECOG scale)		X					X	X ¹⁰	
CBC with diff.		X	X ¹⁹	X ²²	X		X	X	
Prothrombin time (PT) ¹¹	X								
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST); SGPT (ALT); serum creatinine, calcium ²²		X					X	X	
Serum creatinine, phosphorus, uric acid and LDH				X ²²					
LDH, Beta ₂ -microglobulin, C-reactive protein	X								
Electrophoresis of serum and urine		X					X ⁹	X ⁹	
Affected Immunoglobulin ⁸		X					X	X	
Immunofixation serum and urine	X						X ²	X ²	
Immunoglobulin free light chain		X					X	X	
X-ray skeletal survey	X							X ⁴	
Bone marrow aspirate and biopsy, mveloma FISH metanbase	X						X ⁵	X ⁵	

cytogenetics, and flow cytometry									
Mandatory research blood sample (see section 14.1) ^R			X ¹²						
Research bone marrow and blood sample as per 521-93 (Rochester & Florida) or per 919-04 (Arizona), mandatory ^{15,R}	X								
Mandatory research bone marrow Biopsy and aspirate sample (see section 14.1) ^R						X ¹⁴			
Chest x-ray	X								
ECG		X							
Serum pregnancy test		X ³							
Patient Medication Diary ⁷							X	X	
Patient Questionnaire Booklet ²¹		X					X	X	X

- 1) All scheduled visits will have a window of ± 7 days unless otherwise stated.
- 2) Immunofixation (IF) needed only in the absence of M-spike or normalization of FLC.
- 3) For women of childbearing potential only. Must be done ≤ 7 days prior to registration.
- 4) Every 12 cycles (12 months).
- 5) Bone marrow aspirate and biopsy, and flow cytometry only required to document CR and sCR (myeloma FISH and metaphase cytogenetics, are NOT required).
- 6) Doses on Cycle 1 Days 1, 8, 15, and 22 must be given in clinic, and the patient must remain in the clinic for 4 hours to monitor for cytokine release syndrome.
- 7) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
- 8) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient “non-secretory” or if patient has no heavy chain, i.e. light chain myeloma.
- 9) Urine only needed if measurable at baseline. Repeat to confirm CR or progression.
- 10) Physical exam to be repeated at end of first six cycles, then every 3 cycles thereafter.
- 11) Test to be performed for patients on Warfarin only.
- 12) Research blood samples will be drawn on both C1D1 and C2D1 pre-treatment and 4 hours post treatment. In addition, PK samples to be drawn Cycle 1 day 1, per section 14, Tables 14.11 at the following time points: pre-treatment and 0.5hr, 1hr, 2hr, 4hr, 6hr and 24hr post-treatment. **For those patients who go onto receive Cyclophosphamide, PK samples to be collected on Day 1 of the first cycle in which the patient takes both drugs per table 14.22.**

- 13) Patients are required to return to Mayo Clinic every 3 cycles starting with Cycle 7 pre-treatment. Therefore, for the evaluations prior to Cycles 8-9, 11-12, 14-15, etc, the patient may have their tests performed at their local medical doctor (LMD) and the results faxed to the study coordinator for their site.
 - 14) Mandatory research bone marrow will be collected on one of the following: Day 9, 16, or 23 of the cycle that the patient starts cyclophosphamide. MCR & MCF, collect BM aspirates only; AZ to collect BM core and BM aspirates.
 - 15) The patient must be consented and enrolled on study 521-93 or 919-04 in order to participate in this treatment study. Sample collection on 521-93 or 919-04 must occur ≤ 30 days prior to registration.
 - 16) Oxygen saturation should be performed in those patients with the following symptoms at baseline: shortness of breath, dyspnea at rest or upon exertion, tachypnea, new onset of wheezing.
 - 17) Patients are to be monitored for 4 hours in the clinic with vital signs collected pre-dose and 4 hours post dose on Cycles 1 and 2, Day 1.
 - 18) 30 days after last dose of study treatment. Telephone call to patients to assess adverse events only.
 - 19) 4 hours post LCL161 to be collected at the same time as the research blood.
 - 20) N= the first cycle with Cyclophosphamide
 - 21) To be completed prior to treatment. Patient questionnaire booklet must be used; copies are not acceptable for this submission.
 - 22) Weekly labwork can be done at a lab local to the participant
 - 23) Can be done telephonically.
- R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

5.0 Grouping Factor: None**6.0 Registration Procedures**

- 6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (<http://ccswww.mayo.edu/training/>) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Correlative Research**Mandatory**

- 6.21 A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 14.1).

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

An electronically signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB

must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

- 6.4 Prior to accepting the registration, registration application will verify the following:
- IRB approval at the registering institution
 - Patient eligibility
 - Existence of a signed consent form
 - Existence of a signed authorization for use and disclosure of protected health information
- 6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of multiple myeloma at Mayo.
 - Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
 - Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.
- 6.6 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.
- 6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.8 All required baseline symptoms (see Section 10.6) must be documented and graded.
- 6.9 Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Arizona, or Mayo Clinic Florida, under the supervision of a medical oncologist/hematologist.
- 6.9a Study drug is available on site.
- 6.9b Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Treatment medication

Agent	Dose	Route	Day
LCL161**	1200 mg once daily	PO	1, 8, 15, 22
Cyclophosphamide*	500 mg once daily	PO	1, 8, 15, 22

* Cyclophosphamide is added if there is disease progression at any time (confirmation of PD is not required). At the discretion of the treating physician, cyclophosphamide may be added at any cycle after documenting the lack of a minor response by end of Cycle 2 or lack of a partial response by end of Cycle 4 (these responses can be unconfirmed). When adding Cyclophosphamide, new baseline disease measurement will be established. The new baseline disease measurement will be the disease measurement at the end of the cycle prior to the addition of Cyclophosphamide. Cyclophosphamide will be discontinued after 12 cycles of administration. At the physician's discretion, cyclophosphamide may be given IV in 250 mls normal saline over a 30 minute infusion due to the potential for nausea with the oral formulation.

**For patients on LCL161 and Cyclophosphamide, if there is less than a 25% interval reduction in paraprotein, or if nausea is a major problem with the combination, give subsequent doses of LCL161 PO days 2, 9, 16, 23.

For patients being treated with LCL161 + cyclophosphamide, one drug should be administered followed immediately by the second drug. No specific order of administration is required. It is recommended that both medications be taken in the morning. Premedication with an anti-5HT-3 antagonist antiemetic is recommended but not required. These patients will also be required to take prophylactic antibiotics per institutional standards during the course of their treatment with LCL161 due to an increased risk of pneumonia with *Pneumocystis jiroveci*.

LCL161 will be dosed on a flat milligram per dose scale. LCL161 tablets will be administered orally on a weekly schedule. LCL161 doses during Cycle 1, days 1, 8, 15, and 22 must be given in the clinic, and patients must remain in the clinic for 4 hours, to monitor for cytokine release syndrome. At each visit, responsible site personnel will ensure that the appropriate dose of each study drug is administered. Site personnel will provide the patient with the correct amount of LCL161 per cycle for dosing at home. Patients will be instructed to return unused LCL161 study drug to the site at each visit.

- 7.2 The following pre-treatment medications are recommended prior to treatment with LCL161 on days 1, 8, 15 and 22 each cycle but are not required:
- Oral antiemetic
 - Ranitidine 150 mg PO (or equivalent)
 - Acetaminophen 650 mg PO
 - Diphenhydramine 50 mg PO
- 7.3 For this protocol, the patient must return to the consenting institution (Mayo Clinic) for all cycle 1 doses and then for evaluation at least every 28 days during Cycle 2-6. After 6 cycles have been completed patients may return to Mayo Clinic every 3 cycles after confirmation with the treating physician. LCL161 study medication may be supplied to patients for 3 months at a time after Cycle 7 Day 1 (ie, C7D1, C10D1) for those patients who have not experienced a \geq Grade

3 toxicity related to either LCL161 or cyclophosphamide within the previous cycle and is not listed in section 10.41.

7.4 LCL161 Administration

Due to an unknown effect of food on the absorption of LCL161, patients should be instructed to fast for 2 hours prior to taking LCL161 and 2 hours after. Light meals (e.g., cereal, toast and jam for breakfast) and/or liquids (e.g., milk, non-citrus juice) can be taken outside of the fasting periods on days of LCL161 dosing.

For example, if a light meal was completed at 08:00 am, then study drug administration should begin at 10:00 am and the next meal could begin at 12:00 pm. Water and regularly prescribed medications or premedications such as antiemetics are allowed during the fasting periods.

If vomiting occurs during the course of the treatment, no re-dosing of LCL161 is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted appropriately and the exact time of the first episode of vomiting within the first 4 hours post-dose LCL161 on days of PK blood sampling should be recorded appropriately.

Due to a theoretical potential for LCL161 sensitizing skin to toxicity from UV exposure, patients should be instructed to refrain from excessive sun exposure and other forms of UV radiation (e.g., tanning beds) while taking LCL161.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded appropriately.

Due to the possibility of cytokine release syndrome (CRS), the first four doses (Cycle 1) of LCL161 must be administered in the clinic under the supervision of the investigator or his/her designee for 4 hours. If there is no evidence of CRS-like toxicity, at home administration of LCL161 may be appropriate for all subsequent cycles (Cycle 2+). For at home dosing, patients must be informed of the appropriate patient education to ensure awareness of recognizing symptoms of cytokine release syndrome, and an informed action plan in the event of CRS onset. Patients must also be provided with an adequate amount of dexamethasone (2 x 4 mg tablets for a total of 8 mg) in the event of CRS occurrence.

For patients on LCL161 and Cyclophosphamide, if there is less than a 25% interval reduction in paraprotein, give subsequent doses of LCL161 PO days 2, 9, 16, 23

7.5 Local Medical Doctor (LMD) treatment choices:

After Cycle 6 when it has been determined that a patient's malignant disease is stable or objective tumor regression has been observed and the patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be sent with the patient for administration by the patient. The patient will be required to return to Mayo Clinic every 3 cycles. The registering physician retains responsibility for the patient.

8.0 Dosage Modification Based on Adverse Events

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

NOTE: If LCL161 is discontinued, the patient will proceed to event monitoring (see Section 18.0). If the patient is receiving both LCL161 and cyclophosphamide, the patient should continue treatment with LCL161 if cyclophosphamide is discontinued.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.2)

Dose Level	LCL161 once daily Days 1, 8, 15, 22	Cyclophosphamide** once daily Days 1, 8, 15, 22
0*	1200 mg	500 mg
-1	900 mg	400 mg
-2	600 mg	350 mg
-3	300 mg	300 mg

*Dose level 0 refers to the starting dose.

** Only applicable for those patients receiving cyclophosphamide. At the physician's discretion, cyclophosphamide may be given IV in 250 mls normal saline over a 30 minute infusion due to the potential for nausea with the oral formulation.

8.2 Dose Modifications based on adverse event **related** to either LCL161 or cyclophosphamide on Days 8, 15, or 22 of each cycle. Dose reduce only the drug felt to be related to the adverse event.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
SYSTEM ORGAN CLASS	ADVERSE EVENT	AGENT (S)	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENTS ON DAY 8, 15 or 22 OF EACH CYCLE			
Investigations	Grade ≥ 4 neutrophil count decreased	LCL161 Cyclophosphamide	Omit study treatment and follow patient at least weekly until neutrophils $\geq 1.0 \times 10^9/L$ with optimal supportive care. Growth factors can be used to treat neutropenia. If not receiving cyclophosphamide, reduce LCL161 by one dose level. If receiving cyclophosphamide reduce cyclophosphamide one dose level.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

	Grade ≥ 4 platelet count decreased		<p>Omit study treatment and follow patient at least weekly until platelets $\geq 25 \times 10^9/L$ (25,000/mm³)</p> <p>If not receiving cyclophosphamide, reduce LCL161 by one dose level. If symptoms recur, reduce LCL161 by one additional dose level.</p> <p>If receiving cyclophosphamide reduce cyclophosphamide one dose level. If symptoms recur, reduce LCL161 one dose level</p>
	Creatinine increased Grade 2		Continue study treatment at full dose, with optimal supportive care and follow serum creatinine at least twice a week until resolution to Grade ≤ 1 or the patient's baseline.
	Creatinine increased \geq Grade 3		<p>Omit study treatment and follow serum creatinine at least twice a week until resolution to Grade ≤ 1 or the patient's baseline. Restart LCL161 and continue to follow the lab value at least weekly until either resolution or stabilization.</p> <p>If symptoms recur, reduce LCL161 one dose level. For prolonged (>1 week) toxicity that interferes significantly with quality of life, two dose level reductions of LCL161 are allowed.</p>

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
	Alanine aminotransferase increased \geq Grade 3, OR Aspartate aminotransferase increased \geq Grade 3	LCL161	<p>Omit study treatment and follow AST and/or ALT at least twice a week until resolution to Grade \leq 1 or the patient's baseline (i.e. Grade \leq 2 if liver infiltration with tumor present). Restart LCL161 and continue to follow the lab value at least weekly until either resolution or stabilization.</p> <p>If symptoms recur, reduce LCL161 one dose level.</p>
	Blood bilirubin increased \geq Grade 2	LCL161	<p>Omit study treatment and follow AST and/or ALT at least twice a week until resolution to Grade \leq 1 or the patient's baseline (i.e. Grade \leq 2 if liver infiltration with tumor present). Restart LCL161 and continue to follow the lab value at least weekly until either resolution or stabilization.</p> <p>If symptoms recur, reduce LCL161 one dose level.</p>

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

Respiratory, Thoracic and Mediastinal Disorders	Pneumonitis Grade 2	LCL161	Omit study treatment and follow the oxygen saturation measurements at least twice a week until resolution to Grade ≤ 1 or the patient's baseline. A chest radiograph may be used for immediate evaluation; however, it will not replace the need for a chest CT scan. PFTs may also be obtained at the discretion of the investigator to investigate pulmonary toxicity. Restart LCL161 and continue to follow closely for pulmonary symptoms.
	Pneumonitis \geq Grade 3		Omit study medication and follow patient oxygen saturation at least weekly until resolution to Grade ≤ 1 or the patient's baseline. Perform a chest CT scan. Bronchoscopy should be considered to evaluate infectious causes and potentially for biopsy of lung tissue and Pulmonary function testing may be helpful to evaluate the severity of lung disease. Treat as medically indicated (short course of corticosteroids, oxygen, etc). Restart LCL161 and reduce by one dose level upon resolution to Grade ≤ 1 or the patient's baseline

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
Nervous System Disorders	Peripheral sensory neuropathy Grade 2	LCL161	Follow patient at least once weekly until resolution to Grade 1. No dose change is necessary.
	Peripheral sensory neuropathy ≥ Grade 3		Omit LCL161 until recovery to Grade ≤ 2 with optimal supportive care. Reduce LCL161 one dose level.
	Peripheral motor neuropathy Grade 1		Follow patient at least once weekly until resolution to Grade 0. No dose change is necessary.
	Peripheral motor neuropathy ≥ Grade 2		Omit LCL161 until recovery to Grade ≤ 1 with optimal supportive care. Reduce LCL161 one dose level.
Cardiac Disorders	Cardiac Disorders – Other ≥ Grade 3	LCL161	Discontinue study treatment and proceed to event monitoring
Immune system disorders	Allergic reaction ≥ Grade 3	LCL161	Discontinue study treatment and proceed to event monitoring
	Cytokine release syndrome ≥ Grade 3	LCL161	Discontinue study treatment and proceed to event monitoring
	Autoimmune disorder ≥ Grade 3	LCL161	Discontinue study treatment and proceed to event monitoring
Renal and urinary disorders	Cystitis noninfective, ≥ Grade 3	Cyclophosphamide	Omit drugs until adverse event has resolved to grade ≤ 2, reduce cyclophosphamide by two dose levels

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
Other Non-Hematologic events ¹	Grade 3	LCL161 Cyclophosphamide	Omit drugs and follow patient at least weekly until adverse event has resolved to grade ≤ 2 , restart both drugs at next lower dose level.
	Grade 4		Discontinue study treatment and proceed to event monitoring

1) Whenever an inflammatory adverse event is suspected, the investigator is encouraged to obtain a biopsy of the affected organ as long as it does not place the patient at a significantly higher medical risk (e.g., skin biopsies for rash, GI biopsy for chronic diarrhea or bronchoscopic biopsy for suspected pneumonitis are appropriate).

* Located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for the day that is omitted, but treatment may resume once the adverse event has resolved as mandated in Table 8.2. For example, if treatment is omitted on Day 8, but the adverse event has resolved by Day 15, treatment may resume on Day 15.
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.3 A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is $\geq 1000/\mu\text{L}$;
- The platelet count is $\geq 25,000/\mu\text{L}$;
- Any other LCL161 or cyclophosphamide related adverse event that may have occurred has resolved to \leq Grade 2 severity.

If these conditions are not met on scheduled Day 1 of a new cycle, the subject will be evaluated at least weekly and the new cycle of treatment will not be initiated until the adverse event has resolved as described above.

When therapy is resumed it will be considered day one of this new cycle. If LCL161 +/- cyclophosphamide was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If LCL161 +/- cyclophosphamide was omitted for the remainder of the previous cycle or if the new cycle is delayed due to adverse event newly encountered on the scheduled Day 1**, then the scheduled cycle will be started with a one-level dose reduction. If the study drug cannot be restarted within 28 days of the scheduled Day 1 of a given cycle, the patient will be removed from study treatment and will proceed to event monitoring.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no

further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

9.0 Ancillary Treatment/Supportive Care

9.1 Cytokine release syndrome

Cytokine release syndrome (CRS) variably includes signs of flushing or pruritic rash, fever, diarrhea, asthenia/extreme weakness, and in more severe cases, symptomatic hypotension. The symptoms have typically occurred within twelve hrs of LCL161 administration, and if they occur then consideration should be given to increased monitoring/hospitalization, IV fluids, IV dexamethasone, and H1/ H2 receptor antagonists. **Other than for toxicity specifically related to CRS, Dexamethasone should be used sparingly as it may decrease the anti-tumor efficacy of LCL161.**

Before treating a patient with LCL161, all resources required for resuscitation should be immediately available. These include oxygen, resuscitative drugs, appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation. IV fluids and medications for treating hypotension, and nursing staff skilled in the care of acutely ill patients, should also be readily available.

For at home dosing of study drug, patients must be provided with adequate supply of dexamethasone along with instruction on self-administration after contacting (or attempting to contact) the study medical staff. Adequate education on how to recognize the symptoms of cytokine release syndrome should be provided to patients at every cycle. Should CRS onset symptoms occur, patients should be instructed on how to manage the symptoms and to contact the investigator.

9.2 Medications metabolized by CYP3A4/5 (see Appendix III for detailed list)

Results from the clinical DDI study with midazolam CLCL161A2105 showed that LCL161 is a potent time-dependent inhibitor of CYP3A4 activity. For patients taking medications metabolized by CYP3A4/5 and where increased exposure to these medications may put the patient at risk, the medication may be withheld on the day of LCL161 dosing and resumed on the following day. This could include, for example, blood pressure medications metabolized primarily by CYP3A4/5. **High levels of anti-hypertensive medication after LCL161 dosing could exacerbate clinical symptoms of hypotension for patients who develop CRS.** The risk of CRS appears to be limited to the day of LCL161 dosing and CYP enzyme activity returns quickly.

9.3 The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Immunosuppressants, including corticosteroids (except low dose corticosteroids (e.g., prednisone up to but no more than 10 mg p.o. q.d. or its

equivalent) for symptom management and comorbid conditions). The use of dexamethasone is allowed only immediately following the development of CRS.

- Any external beam radiotherapy

9.4 All patients should be treated prophylactically with 5-HT3 antagonist anti-emetics and antibiotics per institutional standard for an increased risk of pneumonia with *Pneumocystis jirovecii*. In addition, pretreatment with any of the meds listed below are recommended but not required:

- H2 blocker such as ranitidine (or equivalent)
- Acetaminophen
- Diphenhydramine or other antihistamine

9.5 Rash

Preclinical data indicate that LCL161 induces apoptosis of basal and suprabasal epidermal cells. Rash, often described as acneiform and sometimes associated with pruritus or some peeling, has been observed in patients treated with LCL161. Symptomatic treatment with topical agents may include steroids.

9.6 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol July 1, 2006, vol. 24 no. 19 3187-3205.

9.7 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.8 Diarrhea: Patients should have medication available in case LCL161-induced diarrhea occurs. Severe (Grade 3 or 4) diarrhea with LCL161 is very uncommon and if it is observed other causes should be suspected and investigated. The commonly used anti-diarrheal medication loperamide is metabolized by CYP2C8 and CYP3A4, and based upon DDI studies performed to date LCL161 may affect the metabolism of loperamide. However, extensive clinical experience with loperamide has demonstrated a wide safety margin for dosing, with very few serious consequences of overdosing. Nonetheless, caution should be used and patients taking LCL161 should be made aware of the risk of constipation.

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe

nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

- 9.9 Pneumonitis: All patients reporting respiratory symptoms should be evaluated for possible infectious causes and for non-infectious pneumonitis. Such symptoms might include cough, dyspnea, fever and in the more severe cases hypoxia. Radiographic confirmation and an appropriate evaluation for infectious causes are required for those patients in whom a diagnosis of pneumonitis is being considered. Bronchoscopy and pulmonary function testing may be helpful in evaluating the causes and severity of lung disease. Initial treatment for pneumonitis should include prednisone at 1 mg/kg/day or similar corticosteroid to be tapered as symptoms resolve (see table 8.2 for LCL161 dosing guidance for pneumonitis).

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web [site](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm): (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

- 10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

- 10.13 Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results

constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

- 10.14 Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other

investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting-

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312) NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64) An adverse event is considered serious if it results in ANY of the following outcomes: <ol style="list-style-type: none"> 1) Death 2) A life-threatening adverse event 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions 5) A congenital anomaly/birth defect. 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6). 		
ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.		
Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	
NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.41 of the protocol. Expedited AE reporting timelines are defined as: <ul style="list-style-type: none"> ○ “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report. ○ “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE. 		
¹ Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: Expedited 24-hour notification followed by complete report within 3 calendar days for: <ul style="list-style-type: none"> • All Grade 3, 4, and Grade 5 AEs Expedited 7 calendar day reports for: <ul style="list-style-type: none"> • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization 		
Effective Date: May 5, 2011		

Additional instructions:

1. Use paper Adverse Event Expedited Report – Single Agent or Multiple Agents report available in forms packet (AdEERs). Fax a copy of the AdEERs report and the Novartis SAE coversheet to the local Novartis Drug Safety & Epidemiology (DS&E) Department at 1-888-299-4565 within 24 hours of the event. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis DS&E Department within 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious

adverse events. The original and the duplicate copies of the AdEERs form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The AdEERs form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax (507-538-7164) to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System or paper form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted.

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report or notification form may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures **MUST BE SPECIFIED BELOW** and will supercede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported
General disorders and administrations site conditions	Fatigue	Grade 3
	Nausea	Grade 3

Gastrointestinal Disorders	Vomiting	
	Diarrhea	
Investigations	Neutrophil count decreased	Grade 3 and Grade 4
	White blood cell count decreased	
	Platelet count decreased	
	Lymphocyte count decreased	
	Aspartate aminotransferase increased	
	Alanine aminotransferase increased	
Blood and lymphatic system disorders	Anemia	Grade 3 and Grade 4

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event, except in the event of a hospitalization (follow reporting instructions for section 10.4).

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting-

10.55 Pregnancy

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

10.6

Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
General disorders and administrations site conditions	Fatigue	X	X
	Fever (Pyrexia)	X	X
	Edema limbs	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of stools	X	
	Diarrhea		X
	Constipation		X
	Abdominal pain	X	X
Skin and subcutaneous tissue disorders	Pruritus	X	X
	Rash maculo-papular	X	X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Blood and lymphatic system disorders	Anemia	X	X
	Febrile neutropenia	X	X
Immune System Disorders	Cytokine release (CRS)	X	X
Nervous System Disorders	Peripheral motor neuropathy	X	X
	Peripheral sensory neuropathy	X	X
Metabolism and nutrition disorders	Anorexia	X	X
Respiratory, thoracic and mediastinal disorders	Dyspnea	X	X
	Cough	X	X
	Pneumonitis	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation – The International Myeloma Working Group (IMWG) uniform response criteria (Rajkumar et al, 2011) will be used to assess response to therapy.

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β -region (usually IgA M-proteins)
- Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
- Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that

patient to assess response. SPEG derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

In addition, for each response category, there will be an “unconfirmed” response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation “u” will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.
 - Serum M-protein ≥ 1 g/dl
 - Urine M-protein ≥ 200 mg/24 h
 - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
 - Bone marrow plasma cells $\geq 30\%$
 - Measurable (≥ 2 cm) plasmacytoma that has not been radiated.

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not “measurable” as above, and the baseline level of the involved FLC is “measurable.”** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. *Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine m-spike) should be the only ones who are evaluated using FLC response criteria. The others should follow*

usual criteria and ignore FLC results with the exception of defining stringent complete response.

- **Evaluable disease:** Patients who do not have a “measurable” serum M-spike, serum free light chain, or urine M-spike.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had “measurable” serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2					
Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated ^{1,2})					
On Study Baseline Value	SPEP ⁴	24 hr UPEP ²	Ig FLC	BM Bx	CT Scan
Serum monoclonal protein ≥ 1 g/dl, and urine M-spike ≥ 200 mg/24 hrs	X	X			
Serum monoclonal protein ≥ 1 g/dl, but urine M-spike < 200 mg/24 hrs	X				
Serum monoclonal protein < 1 g/dl, and urine M-spike ≥ 200 mg/24 hrs		X			
Serum monoclonal protein < 1 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥ 10 mg/dL			X		
Serum monoclonal protein < 1 g/dl, urine M-spike < 200 mg/24 hrs, involved Ig FLC is < 10 mg/dL, bone marrow $\geq 30\%$ plasma cells				X ³	
Measurable plasmacytomas					X

¹ **SPEP, UPEP, immunofixation studies of both serum and urine, and bone marrow biopsy** are required to document CR regardless of registration values, and in addition **FLC measurement and bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

² For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category.

³ At a minimum, a bone marrow biopsy should be repeated every 3 months until document response. Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response).

⁴ If serum monoclonal protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements, however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2.

11.4 Bone progression

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5. Although the definition for “relapse from CR (or sCR) is listed, this will be documented as a response category in ONLY those protocols evaluating disease free survival.

Table 11.5	
CATEGORY	RESPONSE CATEGORY ^a
Stringent Complete Response (sCR) ^b	<ul style="list-style-type: none"> • CR as defined <i>plus</i> • Normal FLC ratio <i>and</i> • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry ⁱ
Complete Response (CR) ^b	<ul style="list-style-type: none"> • Negative immunofixation of serum and urine ^c <i>and</i> • Disappearance of any soft tissue plasmacytoma <i>and</i> • <5% PCs in Bone Marrow <i>and</i> • If the only measurable disease is FLC, a normal FLC ratio ^d
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> • Serum and urine M-component detectable by immunofixation but not on electrophoresis ^c <i>or</i> • ≥90% reduction in serum m-component and urine m-component <100 mg/24 h ^c • If the only measurable disease is FLC, a ≥90% reduction in the

	difference between involved and uninvolved FLC levels
Partial Response (PR)	<ul style="list-style-type: none"> • If present at baseline, $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein or to <200 mg/24hrs^c • If the only measurable disease is FLC, a $\geq 50\%$ reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a $\geq 50\%$ reduction in BM PC's (provided the baseline PC's was $\geq 30\%$) • If present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	<ul style="list-style-type: none"> • If present at baseline, $\geq 25\%$ but $< 49\%$ reduction of serum M protein <i>and</i> reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours^c <i>and</i> • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma <i>and</i> • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease (PD) ^{b, h}	<p>Increase of 25% from lowest value in any of the following^{f, g}:</p> <ul style="list-style-type: none"> • Serum M-component (absolute increase must be ≥ 0.5 mg/dL) <i>and/or</i> • Urine M-component (absolute increase must be ≥ 200 mg.24 hrs) <i>and/or</i> • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) <i>and/or</i> • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be $> 10\%$)^e <p>Or any one or more of the following:</p> <ul style="list-style-type: none"> • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR or PD

^a All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at anytime before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u'] to designate first time point at which response category MAY have been achieved if confirmed.

^b CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

^c If more than one M protein spikes meet the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

^d In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

^e Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

^f A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-component is ≥ 5 g/dL, an increase in serum M-component of ≥ 1 g/dL is sufficient to define disease progression.

^g In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

^h Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

ⁱ Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

12.0 Descriptive Factors

- 12.1 Parameters of hematologic response: serum M-spike ≥ 1 g/dL (distinguish between SPEP measurement versus quantitative IgA measurement) vs urine M-spike ≥ 200 mg/24 hours vs serum M-spike ≥ 1 g/dL and urine M-spike ≥ 200 mg/24 hours vs involved serum immunoglobulin free light chain ≥ 10 mg/dL vs bone marrow plasma cells $\geq 30\%$ vs measurable plasmacytoma that has not been radiated.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 Patients who are sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) will continue treatment per protocol. Note: Cyclophosphamide is discontinued after 12 cycles of administration.
- 13.2 Patients who develop progressive disease (confirmation of PD is not required) while receiving LCL161 alone will continue treatment with the addition of cyclophosphamide. Patients who do not achieve an MR (or uMR) by the end of cycle 2 or a PR (or uPR) by the end of cycle 4 (these responses can be unconfirmed) while receiving LCL161 alone will continue treatment with LCL161 either alone, or with the addition of cyclophosphamide, at the discretion of the treating physician.
- 13.3 Patients who develop progressive disease (confirmed or unconfirmed per physician discretion) **despite the addition of cyclophosphamide** while receiving LCL161 will go to the event-monitoring phase per Section 18.0.

- 13.4 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.5 Criteria for Patient Discontinuation of Protocol Treatment

Patients may discontinue protocol treatment and go to the event-monitoring phase for the following reasons:

- Progressive multiple myeloma
- Patient withdraws consent to continue in the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over a period of 14 days)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early.

13.6 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

- 13.7 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

- 13.8 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated such that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol.
- 13.9 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.
- 13.9a Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

14.0 Body Fluid Biospecimens**Table 14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol**

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Visit 1 (C1D1) Pre Treatment & 4hr Post-Treatment	Visit 2 CN* Day 9 or Day 16 or Day 23	Visit 3 (C2D1) Pre-Treatment & 4hr Post Treatment	Visit 4 (CN*D1) Day 1 of first cycle in which patients take LCL161 + Cyclophosphamide	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Changes in serum IL8 and MCP1; and changes in immune cell subsets	Mandatory	Plasma	Sodium Heparin Green Top	10 mL (2)	X		X	X**	No	Refrigerate, Cold Pack
Pharmacokinetics	Mandatory	Plasma	EDTA (purple top)	2mL	See Table 14.11 for time points			See Table 14.12 for time points***	Yes	See section 14.33
Bone Marrow Bx and Aspirate	Mandatory ****	BM	ACD (yellow top) and BM core Bx	10 mL and (1) BM core Bx		X			No	Ambient

*N = first cycle in which patients take LCL161 + cyclophosphamide.

** To be collected pre-treatment and 4 hours post treatment

***Arizona only

Table 14.11 Pharmacokinetic Sampling Schedule for Single Agent Treatment with LCL161

Table 14.12 Pharmacokinetic Sampling Schedule for Combination Treatment with LCL161 and Cyclophosphamide to be collected on day 1 of the first cycle in which patients take both drugs**

Cycle	Day	Scheduled time point relative to dosing	PK Collection # (LCL161)	Sample # (LCL161)	PK Collection # (CP)	Sample # (CP)	Blood Volume (mL)
<i>N</i> *	1	Pre-dose ^a	101	101	201	201	2
<i>N</i> *	1	0.5h post-dose (±5 min)	101	102	201	202	2
<i>N</i> *	1	1h post-dose (±5 min)	101	103	201	203	2
<i>N</i> *	1	2h post-dose (±5 min)	101	104	201	204	2
<i>N</i> *	1	4h post-dose (±30 min)	101	105	201	205	2
<i>N</i> *	2	24h post-dose (±1 h)	101	107	201	208	2

a. Collect PK sample immediately prior to the start of administration.
**N* = first cycle in which patients take LCL161 + cyclophosphamide.
**** Arizona only

14.2 Collection and Processing

14.21 Degradation of cIAP1 in PBMC, changes in serum IL8 and MCP1

PBMC and Plasma specimens will be collected per schedule and directions as outlined in Blood and Body Fluid Specimens (Section 14.1). Collect 2 x 10 mLs of Sodium Heparin Green Top blood. Centrifuge the blood at 3000 rpm x 10 minutes. Carefully aliquot the 1.0 mL of plasma into three aliquots and freeze/store at - 80°C. Remove the buffy coat and separate the MNC using a standard Ficoll Hypaque methodology.

14.22 Bone Marrow aspirate for gene expression (RNASeq), DNA copy number alterations (aCGH), and somatic mutations (Whole Exome Sequencing).

- On Day 9, 16, or 23 of the cycle that the patient starts cyclophosphamide
 - Collect Bone Marrow aspirate per institution standards
 - Place in 10mL ACD tube.

14.23 Pharmacokinetic Sampling

All blood samples will be taken either by direct venipuncture or an indwelling cannula inserted in a forearm vein. On days and time points when biomarker and PK blood samples are to be obtained, the PK blood sample must be drawn first.

At the specified time points, 2 mL blood draws will be collected into tubes containing EDTA. Immediately after blood collection, the EDTA tube will be gently inverted several times to mix contents and prevent clotting. EDTA tubes containing blood may be kept in an ice water bath at 4 °C for ≤ 60 minutes during the sampling period. Tubes will be centrifuged at 1500 x g at 4 °C for 10 minutes to separate plasma. Immediately after centrifugation, plasma will be transferred into labeled 2 mL polypropylene screw-cap tubes. Plasma will be placed in an upright position at ≤ -20 °C until shipment to the central laboratory. For all PK blood collections, samples collected within the first 2 hours post-dose may be collected within ±5 minutes from the scheduled time point, while samples collected up to 8 hours post-dose may be collected within ±30 minutes from the scheduled time point. Samples collected at 24 hours post-dose or later may be collected within ±1 hours from the scheduled time point.

Refer to the Laboratory Manual for detailed instructions for the collection, handling, storage, and shipment of PK samples.

14.3 Shipping and Handling

14.31 Kits will not be used for this study.

14.32 Shipping Specimens

14.321 Verify ALL sections of the Specimen Submission Forms (i.e. blood, bone marrow – see Forms Packet) are completed and filled in correctly.

14.322 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY**, to:

For Arizona and Florida:
Greg Ahmann
Mayo Clinic, CRB 3-028
13400 E. Shea Blvd.
Scottsdale, AZ 85259

For Rochester:
Kim Henderson
Mayo Clinic, Stable 628

Do not collect or send samples the day before, the day of, or the observed day of a national holiday.

All specimens must be collected and shipped Monday – Thursday ONLY.

14.33 Refer to the Laboratory Manual for detailed instructions for the handling and shipment of PK samples

14.4 Background and Methodology

14.41 Blood samples will be obtained before and four hours after the first dose, and before the fifth dose to determine degradation of cIAP1 in PBMC, changes in serum IL8 and MCP1, and changes in immune cell subsets by flow cytometry. Blood samples will be processed and viably frozen for subsequent analysis to include flow cytometry (plasma cell, dendritic cell, T cell and NK cell subsets) and dendritic cell function (mixed lymphocyte reaction), T cell function (non specific proliferation) and NK cell function (cytotoxicity).

14.42 A baseline bone marrow before treatment will be obtained in all patients per section 4.0. A mandatory bone marrow per Table 14.1 will also be obtained in willing patients. MM cells will be purified by CD138+ selection and RNA and DNA extracted for gene expression (RNASeq), DNA copy number alterations (aCGH), and somatic mutations (Whole Exome Sequencing). This is seen in the majority of patients with hyperdiploid MM. Given the promiscuous array of mutations that activate this pathway, activation of the pathway and comprehensive identification of the mutations is best achieved by the combination of RNAseq, aCGH and WES.

15.0 Drug Information

15.1 LCL161

- 15.11 **Background:** LCL161 is an orally bioavailable, monomeric small molecule IAP antagonist. LCL161 binds to the BIR3 domain of XIAP, CIAP1 (and likely CIAP2) and induces the autoubiquitination and proteasome-mediated degradation of CIAP1. Degradation of CIAP1 is an important marker of LCL161 activity in cell lines. LCL161 treatment of cell lines results in a pulse of NF- κ B activity and cytokine release. This effect is the dose limiting toxicity of cytokine release syndrome observed in some patients treated with the highest doses.
- 15.12 **Formulation:** LCL161 is available for oral administration as 300 mg film-coated tablets.
- 15.13 **Preparation and storage:** LCL161 are stored in standard HDPE bottles with induction seal and child resistant screw cap closures. LCL161 should not be stored above 25 °C.
- 15.14 **Administration:** Patients should be instructed to fast for 2 hours prior to taking LCL161 and for 2 hours after dose administration. Light meals (cereal, toast and jam for breakfast) and/or liquids (eg., milk, non-citrus juice) may be ingested outside of the fasting periods on days of LCL161 dosing. If vomiting occurs no re-dosing of LCL161 is permitted prior to the next scheduled dose. Patients should refrain from excessive sun exposure and other forms of UV radiation (tanning beds). Refer to Treatment Section (7) for specific administration instructions.
- 15.15 **Pharmacokinetic information:**
- a) Absorption – Bioavailability following oral administration was: 52.7% in rats, 100% dogs, and 10-11.6% monkeys. Time to peak serum levels ranged from 0.5 to 6 hours.
 - b) Distribution – Volume of distribution at steady state is moderate to high in all species evaluated, indicating a wide tissue distribution. LCL161 is widely distributed to most tissues following oral administration with the highest exposures other than GI tract observed in melanin-containing tissues (uvea and pigmented skin), liver, adrenals, pituitary, and kidney.
 - c) Metabolism – Major metabolic pathway in human liver in vitro involves cytosolic NADPH-dependent carbonyl reductase, as well as minor contributions by CYP enzymes mainly CYP2C8 followed by CYP3A.
 - d) Excretion – The terminal elimination half-life is 4-16 hours in humans. Elimination is mainly via the feces (70%) in rat (biliary 54%). Urinary elimination accounted for 21%.

15.16 Potential Drug Interactions:

Cytochrome P450 Effect: P-gp substrate. It does not inhibit P-gp, BCRP or MRP2.

Inhibits: CYP3A4/5, CYP2B6, and CYP2C8.

Inducer: LCL161 transiently induces CYP3A activity (study CLCL161A2105) and is unlikely to induce transporters in humans.

Decreased Effect: A trend of decreased activity and mRNA levels was observed for some CYP enzymes including CYP2B6, CYP2C8, CYP2C9 and CYP2C19. A trend of decreased activity of CYP3A was observed, likely due to strong time-dependent inactivation of CYP3A.

15.17 Known potential toxicities: Reversible inflammatory changes have been observed, including changes to mesenteric, mandibular lymph nodes, spleen, skin, bone/joints, bone marrow, serosa/adventitia of thoracic, abdominal and subcutaneous organs or tissues, lungs, GI tract and liver.

Most commonly observed toxicities include: vomiting (51%), nausea (43%), fatigue (30%), constipation (31%), dizziness (25%), cytokine release syndrome** (17%), diarrhea (15%), and decreased appetite (13%).

**Cytokine release syndrome was observed as a dose-limiting toxicity. CRS is consistent with the known mechanism of action of LCL161 which includes activation of the transcription factor NF-kB. Most patients developed symptoms within 5 hours after dosing. Symptoms included flushing, rash, fever, vomiting, diarrhea, asthenia, and symptomatic hypotension. Symptoms generally resolved within hours of onset.

Please see the Investigator's Brochure for more comprehensive toxicity information.

15.18 Drug procurement: Drug will be provided free of charge to patients by Novartis.

Drug accountability: Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

15.19 Nursing Guidelines:

15.191 Instruct patients that they should not eat 2 hours before and

2 hours after LCL161 dose.

- 15.192 Gastrointestinal side effects have been seen with nausea and vomiting being common. Treat symptomatically and monitor for effectiveness. Additionally instruct patients not to repeat doses that are vomited.
- 15.193 Patients should be warned to avoid excessive sunlight or other UV exposure. Drug can cause hyperpigmentations.
- 15.194 Monitor patients for cytokine release syndrome. Symptoms can include flushing, rash, fever, vomiting, diarrhea, asthenia and symptomatic hypotension. These symptoms usually appear within hours of dosing and will usually resolve within hours of onset. Instruct patients to report these symptoms to the study team as soon as possible. Provide patients with dexamethasone for possible administration at home after contacting medical staff to report their symptoms. Dexamethasone or other steroids (excepting topical and inhaled steroids) should be used very sparingly, as it is expected to suppress any immune stimulatory benefit of LCL161 in myeloma.
- 15.195 Patients may experience inflammatory changes to the mesentery, mandible, lymph nodes, spleen, skin, bone/joints, bone marrow, serosa/adventitia of the thoracic, abdominal and subcutaneous organs or tissues, lungs GI tract and liver. These changes are usually reversible.
- 15.196 Fatigue is common. Instruct patient in energy-conserving lifestyle.

15.2 **Cyclophosphamide for Oral Administration (Cytosan®, Neosar®, CTX)**

- 15.21 **Background:** Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunomodulatory activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.
- 15.22 **Formulation:** Commercially available for oral administration as:
Tablets: 25 mg, 50 mg
- 15.23 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature preferably below 25°C (77°F). This product will withstand brief exposure to temperatures up to 30°C (86°F), but should be protected from temperatures above 30°C (86°F). Dispense in a tight container as defined in the USP/NF. Refer to labeling on the bottle for expiration date of the commercial tablets.
- 15.24 **Administration:** Instruct patients to take in the am on days 1, 8, 15, and 22 each cycle for those patients taking cyclophosphamide per protocol.

To be taken in a at the same time each day, preferably in the morning. Tablets are not scored and should not be cut or crushed. To minimize the risk of bladder irritation, do not administer tablets at bedtime.

15.25 **Pharmacokinetic information:**

Distribution: V_d : 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)

Protein binding: 10% to 60%

Bioavailability: >75%

Time to peak, serum: Oral: ~1 hour

Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard

Half-life elimination: 3-12 hours

Excretion: Urine (<30% as unchanged drug, 85% to 90% as metabolites)

15.26 **Potential Drug Interactions:**

Cytochrome P450 Effect: **Substrate** of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP3A4 (weak); **Induces** CYP2B6 (weak), 2C8 (weak), 2C9 (weak)

Increased Effect/Toxicity: Allopurinol may cause an increase in bone marrow depression and may result in significant elevations of cyclophosphamide cytotoxic metabolites. CYP2B6 and CYP3A4 inducers may increase the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inducers. Etanercept may enhance the adverse effects of cyclophosphamide. Cyclophosphamide reduces serum pseudocholinesterase concentrations and may prolong the neuromuscular blocking activity of succinylcholine and mivacurium.

Decreased Effect: Cyclophosphamide may decrease the absorption of digoxin tablets. CYP2B6 and CYP3A4 inhibitors may decrease the levels/effects of acrolein (the active metabolite of cyclophosphamide); see package insert for example inhibitors.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:

Dermatologic: Alopecia but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.

Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)

Gastrointestinal: Nausea and vomiting, usually beginning 6-10 hours after administration; anorexia, diarrhea, mucositis, and stomatitis are also seen

Hematologic: Thrombocytopenia and anemia are less common than leukopenia

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Facial flushing

Central nervous system: Headache

Dermatologic: Skin rash

Rare known potential toxicities, <1% (Limited to important or life-threatening):

Cyclophosphamide may potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, malaise, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (e.g., bladder carcinoma), SAIDH, Stevens-Johnson syndrome, toxic epidermal necrolysis, weakness.

- 15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 **Nursing Guidelines:**

- 15.291 Myelosuppression is common. Monitor CBC including platelets. Instruct patient on signs/symptoms of infection and to inform health care team of any unusual bruising, or signs of bleeding.
- 15.292 Instruct patient to drink 2-3 liters of fluid per day for 2-3 days following treatment and to void frequently, not greater than every three hours to facilitate keeping the bladder clear of drug.
- 15.293 Instruct patient to report any urinary urgency, frequency, dysuria, or hematuria.
- 15.294 Advise patient in possible strong metallic taste associated with cyclophosphamide and suggest hard candy with a strong flavor (cinnamon, peppermint) to alleviate it.

- 15.295 Administer antiemetics as necessary to minimize nausea and vomiting, which usually occurs 6-8 hours after administration.
- 15.296 Report and record any complaint of lightheadedness, facial “heat sensation,” diaphoresis during administration.
- 15.297 Use of an ice cap may be helpful in preventing or limiting alopecia.
- 15.298 Corticosteroids, phenothiazine, imipramine, vitamin A succinylcholine, digoxin, thiazide diuretics, warfarin and allopurinol may inhibit cyclophosphamide metabolism and modify its’ effect. Concomitant administration of these medications may also increase bone marrow suppression.
- 15.299a Advise female patients of possible menstrual changes or amenorrhea.
- 15.299b Patients on anticoagulant therapy should have INR levels carefully monitored as cyclophosphamide increases their effect.
- 15.299c Monitor electrolytes and for signs/symptoms of SIADH and tumor lysis syndrome.
- 15.299d Monitor digoxin levels closely as cyclophosphamide may decrease these levels.
- 15.299e Cyclophosphamide may potentiate doxorubicin-induced cardiomyopathy. Instruct patient to report any chest pain.

16.0 Statistical Considerations and Methodology

- 16.1 Overview: This study will assess the efficacy and adverse event profile of LCL161 in patients with relapsed multiple myeloma using a one-stage phase II study design. This study will also explore the efficacy and adverse event profile of LCL161 in combination with cyclophosphamide following lack of response or progression on LCL161 alone.
- 16.11 Primary Endpoint: The primary endpoint of this trial is the proportion of confirmed overall responses (sCR, CR, VGPR, or PR) with single agent LCL161. Confirmed overall response rate will be evaluated using the

LCL161 alone treatment period. Throughout Section 16.0, confirmed overall response will be considered synonymous with “success”, unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for confirmed overall response, with the exception of patients who are determined to be a major treatment violation.

- 16.12 **Sample Size:** The one-stage study design to be used is fully described below. Twenty-five evaluable patients are required to assess the primary endpoint. We anticipate accruing an additional 2 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum total sample size will be 27 patients.
 - 16.13 **Accrual Rate and Study Duration:** Based on prior Mayo Clinic accrual in this patient population we expect an accrual of about 3-4 patients per month. Therefore, accrual to this study should take about 9-12 months. The analysis can begin as soon as the last patient has been observed for at least 6 months, or about 15-18 months after the trial opens.
- 16.2 **Statistical Design**
- 16.21 In a recent phase I study of MLN9708 (a next generation proteasome inhibitor that is given orally), 2 patients (11%) out of 18 response-evaluable patients experienced a response (1 VGPR, 1 PR; Kumar et al, 2012). Thus, in the current study, the largest success proportion where the proposed treatment regimen (single-agent LCL161) would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following one-stage binomial design requires 25 patients to test the null hypothesis that the true success proportion in this patient population is at most 10%.
 - 16.211 **Final Decision Rule:** If 4 or fewer successes are observed in 25 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 5, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.
 - 16.212 **Over Accrual:** If more than the target number of evaluable patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.
 - 16.22 **Power and Significance Level:** Assuming that the number of confirmed overall responses is binomially distributed, with a significance level of 10%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various success proportions can be

tabulated as a function of the true success proportion as shown in the following table.

If the true confirmed response rate is	0.10	0.15	0.20	0.25	0.30	0.35
then the probability of declaring that LCL161 alone warrants further studies is . . .	0.10	0.32	0.58	0.79	0.91	0.97

- 16.23 Other Considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.
- 16.3 Analysis Plan: The analysis for this trial will commence at planned time points (see Section 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is approximately 15 months after the trial begins, i.e., as soon as the last patient has been observed for at least 6 months.
- 16.31 Primary Endpoint
- 16.311 Definition: The primary endpoint of this study is the proportion of confirmed overall responses with single agent LCL161 (prior to initiation of cyclophosphamide). A confirmed overall response is defined as sCR, CR, VGPR, or PR noted as the objective status on two consecutive evaluations while receiving single agent LCL161. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major treatment violation.
- 16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. 95% confidence intervals for the true success proportion will be calculated by the exact binomial method.
- 16.32 Definitions and Analyses of Secondary Endpoints
- 16.321 Confirmed overall response rate with the addition of cyclophosphamide: The confirmed overall response rate for LCL161 with the addition of cyclophosphamide for lack of response or progression will be estimated by the number of patients who achieve a confirmed overall response at any time (with single agent LCL161 or LCL161 plus cyclophosphamide) divided by the number of evaluable patients. 95% confidence intervals for the true confirmed overall response rate will be

calculated by the exact binomial method. In addition, the number of patients who did not achieve a confirmed overall response with LCL161 alone then had a confirmed overall response after the addition of cyclophosphamide to LCL161 will be evaluated.

16.322 Overall survival: Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958). All evaluable patients will be included in this analysis.

16.323 Event-free survival: The event-free survival time is defined as the time from registration to disease progression while receiving LCL161 and cyclophosphamide, death due to any cause, or subsequent treatment for multiple myeloma. Date of progression will be defined as the date that the criteria for progressive disease (per section 11.5) were first met after initiation of cyclophosphamide. If a patient goes off study treatment and never received cyclophosphamide, they will be censored on the date they went off study treatment. If a patient initiates cyclophosphamide but later discontinues cyclophosphamide due to toxicity and continues LCL161 alone, disease progression on LCL161 alone will be considered an event in this case. The distribution of event-free survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958). All evaluable patients will be included in this analysis.

16.324 Adverse Events: The maximum grade for each type of adverse event, regardless of causality, will be recorded and reported for each patient, and frequency tables will be reviewed to determine adverse event patterns. Adverse events will continue to be recorded and reported up to 30 days after the last day of study drug treatment.

16.33 Definitions and Analyses of Correlative Endpoints

16.331 Analysis of cIAP1, serum cytokines, immune cell subsets by flow cytometry, and activating mutations of the NFkB pathway: Statistical analysis of each biomarker will be primarily descriptive. Continuous biomarker levels will be explored in a graphical manner including mean plots and plots of change and percent change from baseline and other summary measures. Any potential relationships between the baseline level or change in the level of each biomarker and clinical outcome such as confirmed overall response, 6-month progression-free survival, and adverse event incidence will be further analyzed using Wilcoxon rank sum tests or logistic regression methods, as appropriate. Association between a mutation status and confirmed overall response will be assessed using a chi-squared

test. Comparisons with 1-sided p-values ≤ 0.10 are considered significant. As this translational component is exploratory in nature, we have not adjusted for multiple comparisons.

16.332 Analysis of Patient-Reported Outcomes (Quality of Life and Symptoms)

Patient-reported outcomes (quality of life and symptoms) will be assessed prior to review of treatment response and discussions of patient's general health since last treatment evaluation.

A paper booklet containing all the patient-reported outcomes will be administered in clinic at baseline and every cycle visit at Mayo Clinic, and each PRO will be scored according to the published scoring algorithm. Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Changes from baseline at each cycle will be statistically tested using paired t-tests, and standardized response means (mean of the change from baseline scores at a given cycle, divided by the standard deviation of the change scores) will be interpreted (after applying Middel's (2002) adjustment) using Cohen's (1988) cut-offs: <0.20 = trivial; 0.20 - <0.50 = small; 0.50 - <0.80 = moderate; and ≥ 0.80 = large. Correlation between outcomes will employ Pearson and/or Spearman correlations at individual time points.

- 16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.4 Data & Safety Monitoring

- 16.41 The principle investigator(s) and the study statistician will review the study at least every quarter to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.
- 16.42 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with

attribute specified as “possible,” “probable,” or “definite”) that satisfy any of the following:

- if 4 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event (including all cycles of treatment with LCL161 or the combination of LCL161 and cyclophosphamide)
- if after the first 15 patients have been treated, 25% of all patients experience a grade 4 or higher non-hematologic adverse event (including all cycles of treatment with LCL161 or the combination of LCL161 and cyclophosphamide)
- if 6 or more patients treated with the LCL161 and cyclophosphamide combination experience a grade 4 or higher non-hematologic adverse event after starting the combination

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

- 16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 15 months after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has been observed for 6 months.
- 16.6 Inclusion of Women and Minorities
- 16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.
- 16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.
- 16.63 The geographical region served by Mayo, has a population which includes approximately 3% minorities. Based on prior Mayo studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	9	17	26
Ethnic Category: Total of all subjects	9	18	27
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	8	17	25
Racial Category: Total of all subjects	9	18	27

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

16.7 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis’ responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations.

Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s) -

Case Report Form (CRF)	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
Pretreatment Measurement Form	
SPEP, UPEP, FLC , Serum and Urine Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey, Cytogenetic, FISH on study reports	
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet	Submit ≤2 weeks after registration - Patient questionnaire booklet must be used; copies are not acceptable for this submission.
Patient Questionnaire Booklet Compliance Form	Submit ≤ 2 weeks after registration - This form must be completed only if the Patient Questionnaire Booklet contains absolutely NO patient provided assessment information.

Test Schedule Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment Form	X ¹	X
Adverse Event Form	X	X
Treatment Measurement Form	X	X
SPEP, UPEP, FLC , Serum and Urine	X ²	X ²

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Immunofixation, Bone Marrow biopsy and aspirate, X-Ray skeletal survey		
Research Blood Submission Form	X (see Section 14.0)	
Research Bone Marrow Biopsy and Aspirate Submission Form	X (see Section 14.0)	
Pharmacokinetics (PK) Submission Form	X (see Section 14.0)	
End of Active Treatment/Cancel Notification Form		X
Patient Questionnaire Booklet ³	X	X
Patient Questionnaire Booklet Compliance Form ⁴	X	X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)	
ADR/AER	At each occurrence (see Section 10.0)	

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Submission of these reports is only required for documentation of CR or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation of progression, submit one report for one of the measures where progression was seen. Attention: QAS for MC1381.
3. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission. To be completed prior to treatment every cycle; and at end of study treatment.
4. This form must be completed **only** if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.

Follow-up Material(s) -

CRF	Event Monitoring Phase ¹				
	q. 6 months until PD ²	At PD ²	After PD q. 6 mos.	Death	New Primary
Event Monitoring Form	X	X	X	X	At each occurrence

1. If a patient is still alive 1 year from the end of treatment, no further follow-up is required.
2. Submit copy of documentation of progression (submit one report for one of the measures where progression was seen) to the MCCC Operations Office, Attention: QAS for MC1381.

19.0 Budget

- 19.1 Costs charged to patient: Cyclophosphamide and routine clinical care

19.2 Tests to be research funded: LCL161, mandatory blood samples and optional bone marrow

19.3 Other budget concerns: None

20.0 References

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Appendix I
ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II
Mayo Risk StratificationHigh Risk

FISH deletion 17p

FISH t(4:14)

FISH t(14:16)

Metaphase cytogenetic del 13

Hypodiploidy

PCLI >3%

Appendix III: Concomitant Medications Guidance

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below (Table 1). Prior to initiating the study treatment, the Investigator should carefully review the patient's current medications. Patients must be carefully monitored for potentiation of toxicity due to an individual concomitant medication during the study.

LCL161 has the potential to affect the disposition of concomitant medications metabolized by CYP3A4/5. In vitro data indicate LCL161 is a potent time-dependent inhibitor of CYP3A4/5 ($K_I = 0.8 \mu\text{M}$) and a clinical study with midazolam confirmed this in vitro finding. Results indicated that LCL161 is a potent but transient time-dependent inhibitor of CYP3A4/5, resulting in a 3-fold and 9-fold increase in midazolam C_{max} and $\text{AUC}(0\text{-}\infty)$, respectively, when LCL161 and midazolam were co-administered [Investigator's Brochure]. For patients taking medications metabolized by CYP3A4/5 and where increased exposure to these medications may put the patient at risk, the medication may be withheld on the day of LCL161 dosing and resumed on the following day. Patients taking medications that are CYP3A substrates with a narrow therapeutic index, however, have a serious safety risk and therefore these medications are prohibited during the course of the study. In vitro data also indicate that LCL161 may reversibly inhibit CYP2B6 in vivo ($\text{IC}_{50} = \sim 1 \mu\text{M}$). Therefore, caution should be used with co-administration of CYP2B6 substrates.

The potential for drug interactions that affect LCL161 drug disposition is minimal due to the involvement of several metabolic pathways in the clearance of LCL161. Based on in vitro studies in human liver, the major metabolic pathway for LCL161 is not mediated by CYP450 enzymes, but in-part, by cytosolic NADPH-dependent carbonyl reductase(s), accounting for ~60% of the metabolism of LCL161. The remaining oxidative metabolism occurred mainly through CYP2C8 with minor contributions by CYP3A4. Based on this in vitro data, use of concomitant medications known to be strong inhibitors of CYP2C8 will be prohibited in the study. Caution is recommended when combining LCL161 with any other CYP3A4/5 or CYP2C8 interacting medications.

Although there is no inherent risk for LCL161 to cause QT prolongation based on in vitro and clinical ECG data from study CLCL161A2101 (Investigator's Brochure), it is recommended that caution is exercised with all medications that may produce this effect. In addition, due to the time-dependent inhibition of CYP3A4/5 by LCL161, medications that are known to carry a risk for QT prolongation and are CYP3A substrates are prohibited in this study.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. These lists are not comprehensive and are only meant to be used as a guide. Please contact the medical monitor with any questions.

Table 1: List of prohibited medications

Category	Drug Name
CYP3A4/5 substrates with a narrow therapeutic index (NTI) ¹	Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozone, quinidine, sirolimus, tacrolimus, terfenadine
Strong CYP2C8 Inhibitors	Gemfibrozil
Medications that are known to carry a risk for QT prolongation <u>and</u> are CYP3A substrates	Astemizole, clarithromycin, erythromycin, haloperidol, terfenadine, quinidine
¹ NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).	

Table 2: List of medications to be used with caution¹

Category	Drug Name
Sensitive CYP3A4/5 substrates	Alfentanil, alpha-dihydroergocryptine, aplavivoc, aprepitant, atorvastatin, brexanvir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maravivoc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicrivivoc
CYP2C8 inhibitors	Deferasirox, fluvoxamine, gemfibrozil, ketoconazole, montelukast, trimethoprim
Medications that are known to carry a risk for QT prolongation	Amiodarone, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl, mesoridazine, methadone, moxifloxacin, pentamidine, pimozone, probucol, procainamide, quinidine, sotalol, sparfloxacin, terfenadine, thioridazine, vavdetanib
CYP2B6 substrates	Bupropion ² , cyclophosphamide, efavirenz ² , ifosfamide, methadone, thiotepa
¹ Any drug mentioned in the above list should be contraindicated if they are excluded based on any other exclusion criteria	
² Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when coadministered with a potent inhibitor.	

Appendix IV PATIENT MEDICATION DIARY

Name _____

Mayo Clinic No. _____

Please complete this diary on a daily basis. Write in the amount of the dose of LCL161 and Cyclophosphamide (if applicable) that you took in the appropriate "Day" box. On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

You should fast for 2 hrs prior to taking LCL161 and you should fast again 2 hrs after taking LCL161. Light meals (e.g., cereal, toast and jam for breakfast) and/or liquids (e.g., milk, non-citrus juice) can be taken outside of the fasting periods on days of LCL161 dosing.

For example, if a light meal was completed at 08:00 am, then study drug administration should begin at 10:00 am and the next meal could begin at 12:00 pm. Water and regularly prescribed medications are allowed during the fasting periods.

Week of:

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
LCL161							
Cyclophosphamide							

Week of:

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
LCL161							
Cyclophosphamide							

Week of:

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
LCL161							
Cyclophosphamide							

Week of:

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
LCL161							
Cyclophosphamide							

My next scheduled visit is: _____

If you have any questions, please call: _____

Patient Signature: _____

Date: _____

Area Below Only To Be Completed only by Coordinator

Number of pills returned _____
Date _____

Study Coordinator Initials _____
Discrepancy Yes _____ No _____

Appendix V: Patient Information Sheet and Linear Analog Self-Assessment (LASA)

To order booklets please e-mail Leslie Alfieri at Alfieri.leslie@mayo.edu

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your ‘quality of life’ as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains one set of questions:
 - a. Linear Analog Self Assessment (10 questions)
2. Directions on how to complete the set of questions are written on the top of the set.
3. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

Linear Analog Self-Assessment (LASA)

Directions: Please check the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today.**

How would you describe:

1. your overall Quality of Life?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

2. your overall mental (intellectual) well being?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

3. your overall physical well being?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

4. your overall emotional well being?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

5. your level of social activity?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

6. your overall spiritual well being?

As bad as it can be 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ As good as it can be

7. the frequency of your pain?

No pain 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Constant pain

8. the severity of your pain, on the average?

No pain 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Pain as bad as it can be

9. your level of fatigue, on the average?

No fatigue 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Fatigue as bad as it can be

10. your level of anxiety, on the average?

No anxiety 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ Anxiety as bad as it can be